Temporal Processing in the Visual System

Dr. Ken Nakayama
Dr. John A. Assad

Seyed Mehdi Aghdaee

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Abstract

Encoding time is one of the most important features of the mammalian brain. The visual system, comprising almost half of the brain is of no exception. Time processing enables us to make goal-directed behavior in the optimum "time window" and launch a ballistic eye movement, reach/grasp an object or direct our processing resources (attention) from one point of interest to another. In addition, encoding time is critical for higher cognitive functions, enabling us to make causal inferences.

The limitations of temporal individuation in the visual stream seem to vary across the visual field: the resolution gradually drops as objects become farther away from the center of gaze, where little differences were found in terms of resolution for objects in the upper versus lower visual field. This resolution of temporal individuation is vastly different from the resolution ascribed to spatial individuation. If individuation is mediated through attention, as some researchers have proposed, the general term "attention" seems to possess different properties, at least regarding temporal and spatial processing.

Next we looked at another aspect of encoding time: Temporal Order Judgments (TOJ), where animals had to judge the relative timing onset of two visual events. After training two monkeys on the task, we recorded from neurons in the lateral intraparietal

area (LIP), while the animals reported the perceived order of two visual stimuli. We found that LIP neurons show differential activity based on the animal's perceptual choice: when the animal reports the stimulus inside the receptive field of the neuron as first, the cells show an increased level of activity compared to when the animal reports the same stimulus as second. This differential activity was most reliable in the tonic period of the response (~100 ms after stimulus onset). However, no difference in visual response latencies was observed between the different perceptual choices.

The parietal cortex has previously been implicated in temporal processing based on patient studies as well as neuroimaging investigations. Physiological studies have also suggested the involvement of parietal area in encoding *elapsed* time. However, our study is the first to demonstrate parietal neurons encoding *relative* timing.

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“If you want to do something, you’ve got to do it properly.”

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To Job,

For his patience, perseverance and inspiration,
And the psychological trauma he underwent…

"We can solidly settle our ideas only by trying to destroy our own conclusions by counter-experiments. What is observably true is the only authority. If through experiment, you contradict your own conclusions—you must accept the contradiction—but only on one condition: that the contradiction is proved."

Claude Bernard

Chapter 1

General Introduction

1.1 Why time matters?

Analysis of a scene requires understanding the location of objects as well as the nature of objects in the natural world. However, "what" is "where" does not suffice; occasionally there is a particular time to act upon a stimulus, when acting outside of the optimum time window will not yield the desired goal. Thus an important prerequisite of any information-processing system is to encode time, enabling it to interact with the environment accurately and in a timely manner. In simple terms, we also need to know about the "when".

Many timing computations are of temporal *intervals,* the absolute time that has elapsed between events. Computing time intervals is inherent to behavioral conditioning (Gallistel & Gibbon, 2000) and provides the basis for behavioral rhythms, ranging from sub-seconds to hours (e.g., circadian cycles) (Buhusi & Meck, 2005). For example, rhythmic movements are often initiated in the absence of external cues, and thus must rely on an internal "clock" to keep track of elapsed time (Schneider & Ghose, 2012).

This thesis is instead concerned with *relative timing,* the ordinal comparison of instances of time. One should first distinguish between *implicit* and *explicit* computations of relative timing. Many brain computations involve implicit, "unconscious" relative timing. For example, visual direction selectivity, spike-timing-dependent plasticity, and horizontal sound localization based on binaural time disparity are phenomena in which the output of the computation bears little subjective relation to timing. In the case of binaural time-disparity comparisons for example, the output is the horizontal location of a sound source, and does not have any explicit representation of timing. Implicit relative

timing probably also plays a role in individuating objects: elements in the scene that change together over time, as well as space, are grouped together and become part of the "same object", both in the visual (Alais, Blake, & Lee, 1998) and auditory domains (Bregman, 1990). Implicit relative timing computations are generally based on very brief intervening intervals between events; for example, binaural timing comparisons occur within the membrane time constant of single neurons in the auditory brainstem (Carr & Konishi, 1990).

On the other hand, we also make *explicit* judgments of relative timing. Explicit judgments of temporal order are crucial for many higher cognitive functions. An important example is our ability to draw causal inferences. Causality refers to the relationship of an event (cause) and a second event (effect), in which the second event is understood as a consequence of the first. The modern definition of causality has been attributed to David Hume, who proposed temporal precedence of cause over effect as one of his eight ways of judging whether two events are related as "cause" and "effect" (Selby-Bigge, 1896). That is, if we perceive event B as following event A, it is plausible that A is the cause of B; however, the reverse cannot to true. Thus determining the order of temporal events influences how we establish causal inferences between events. Compared to implicit relative timing, we can determine explicit temporal order over much wider ranges of intervening intervals between events.

1.2 Where is "when" in the brain?

Traditionally the basal ganglia and cerebellum have been implicated in timing processes. This view arose mainly because patients with Parkinson's disease or cerebellar damage often suffer from motor timing abnormalities, along with motor problems (Harrington, Haaland, & Hermanowicz, 1998; R. B. Ivry, Keele, & Diener, 1988; O'Boyle, Freeman, & Cody, 1996; Spencer, Zelaznik, Diedrichsen, & Ivry, 2003). However, neuropsychological and animal lesion studies, as well as functional imaging in healthy human subjects, have shown that that these structures are also involved in timing at a perceptual level (Harrington et al., 1998; R. B. Ivry et al., 1988; Richard B. Ivry & Keele, 1989; Jueptner et al., 1995; Malapani, Dubois, Rancurel, & Gibbon, 1998; Meck, 1996; Rammsayer & Classen, 1997). The role of the cerebral cortices in timing has received comparatively less attention, despite the dense interconnections between the cerebral hemispheres and the basal ganglia and cerebellum (Cavada & Goldman-Rakic, 1991; Tolbert & Bantli, 1979; Yamada & Noda, 1987).

The role of cortical structures in timing was initially mentioned by the British neurologist MacDonald Critchley, who reported timing deficits in patients with damage to the parietal cortex (Critchley, 1953). However, the parietal lobe, in particular the right parietal lobe, gained much more attention in the late 1990s. Husain and colleagues reported that patients with right parietal damage had deficits in an attentional blink task (Husain, Shapiro, Martin, & Kennard, 1997). Harrington and colleagues found deficits in duration perception in individuals with right hemisphere damage; moreover, the subjects' temporal performance was correlated with their ability to direct non-spatial attention

(Harrington et al., 1998). The authors suggested that the right prefrontal-inferior parietal network could be involved in timing judgments.

Battelli and colleagues carried out a series of experiments on parietal neglect patients, and based on their findings, proposed that the right parietal lobe constitutes a "when" cortical visual pathway (Battelli, Pascual-Leone, & Cavanagh, 2007; Battelli, Walsh, Pascual-Leone, & Cavanagh, 2008). Although their experiments did not directly measure time perception, their results are strongly suggestive of timing deficits in neglect patients. Based on data from their previous studies (Battelli et al., 2001; Battelli, Cavanagh, Martini, & Barton, 2003), they proposed that while each parietal lobe is responsible for directing spatial attention to the contralateral visual hemifield, the right parietal lobe is responsible for temporal attention in *both* visual hemifields: patients with right (and not left) parietal damage had bilateral deficits in distinguishing flickering vs. moving (apparent motion) dots in a modified ternus display (Battelli et al., 2001). In another study they also showed that patients with right (and not left) parietal damage had problems identifying a temporal "oddball", a spot of light flickering out-of-phase with other spots in the visual scene (Battelli et al., 2003). Based on these observations, the authors proposed that the right parietal cortex is responsible for identifying the onset and offset transients of elements in the visual scene, and thus linking the offsets and onsets into temporally defined objects.

The parietal lobe is not the only cortical area involved in encoding time: frontal cortex (in particular dorsolateral prefrontal cortex) has been implicated in timing judgments (Harrington et al., 1998; Nenadic et al., 2003; Onoe et al., 2001; Rao, Mayer, & Harrington, 2001). In addition, thalamus (Matell & Meck, 2004; Nagai et al., 2004)

and hippocampus (Meck, 1988; Meck, Church, & Olton, 1984) have also been proposed in temporal judgments. Thus the circuitry underlying time perception appears to involve a distributed network of brain areas, including parietal and frontal cortex, the basal ganglia, cerebellum, thalamus and hippocampus. Different parts of the circuitry are likely involved in different timescales of temporal judgments (sub-second vs. supra-second) and different aspects of timing, such as reproduction vs. perception of time durations (absolute time) as well as onset/offset (relative time) judgments (Jantzen, Steinberg, & Kelso, 2005; Mauk & Buonomano, 2004; Meck & Malapani, 2004; Meck, Penney, & Pouthas, 2008).

1.3 Temporal Order Judgment

Reporting the perceived order of two stimuli is referred to as Temporal Order Judgment (TOJ). Experiments involving judgments of temporal order (or simultaneity) have been historically used to study problems in sensory systems including dependence of sensory latency on stimulus intensity (Roufs, 1963), lateralization of function in the cerebral hemispheres (Kappauf & Yeatman, 1970), identification of speech sounds (Liberman, Harris, Kinney, & Lane, 1961), auditory stream segregation and perception of melodic lines (Bregman & Campbell, 1971) and selective attention (Sternberg & Knoll, 1973).

All TOJ experiments are based on the same logic: systematic differences exist between the objective and subjective simultaneity of a pair of stimuli. These differences

can be indexed by the physical time difference needed for the pair of stimuli to appear simultaneous, or for the two possible orders to be reported with equal frequency. This *constant error* is usually attributed to differences between the arrival times of the signals corresponding to each stimulus at the brain area that judges the temporal order (Sternberg & Knoll, 1973). The "arrival latencies" reflect detection and transmission delays that are not compensated for in perception, and may vary with different attributes of the stimulus, such as contrast and eccentricity of visual stimuli (Sternberg & Knoll, 1973). However, modern neurophysiology has not confirmed the original ideas regarding "arrival latencies" (see 1.4 below).

Attention has always been intertwined with temporal order studies. According to the British psychologist Edward Titchener and his *law of prior-entry* "The object of attention comes to consciousness more quickly than the objects which we are not attending to" (Titchener, 1908). Though experimental psychologists had confirmed the effect of attention on visual (and cross-modal) TOJ, a longstanding debate was whether the attention effects could be attributed to response bias (Pashler, 1998). Using an orthogonal design in which response bias was both reduced and measured, Shore and colleagues asked subjects to judge the order of presentation of two visual stimuli (a horizontal and a vertical line) and found that, although response bias has a large influence, exogenous (and to a lesser extent endogenous) attention cues could still affect the perceived order of visual stimuli (Shore, Spence, & Klein, 2001). Further studies that controlled for response bias have confirmed the existence of prior-entry in vision (Schneider & Bavelier, 2003; Weiss & Scharlau, 2011) as well as in the somatosensory domain (Yates & Nicholls, 2009). It is important to emphasize that here we apply a

broader and more modern interpretation to prior-entry than what Titchener originally proposed. That is, we recognize that attention influences TOJ, though not necessarily by affecting neuronal transmission times.

Localization studies in healthy human subjects suggest the parietal cortex is involved in TOJ tasks. Woo and colleagues used temporary disruptive mechanisms to study TOJ in humans (Woo, Kim, & Lee, 2009). While subjects made order judgments of two stimuli, one in each visual field, the authors applied a single pulse TMS at either the left or right posterior parietal cortex, and found that the processing of the contralateral stimulus was delayed for 20-30 ms, only when TMS was applied on the right, but not on the left side. Interestingly, the disruptive effect was evident only when the TMS pulse was given 50-100 ms after the onset of the first stimulus. Davis and colleagues asked subjects to perform a temporal order judgment vs. shape judgment task of two stimuli (one in each visual hemifield), with the difficulty equated between the two tasks (Davis, Christie, & Rorden, 2009). Using fMRI they looked at differential brain activity between the two tasks among subjects and found bilateral activity in the temporal parietal junction (TPJ). However, a potential confound is that only their TOJ task (and not the shape task) required temporal selectivity. Thus in their follow-up control experiment when they modified their paradigm so that both tasks required discriminating brief events concurrent with the onset of the visual stimuli, they only observed left TPJ activity for the TOJ task. This is contrast with other studies showing a right parietal dominance in TOJ tasks. However, temporally attending and discriminating onset of objects is an inherent aspect of the TOJ task where it is totally discounted in Davis' second experiment (Davis et al., 2009).

Patient studies also point to a role for the parietal cortex in TOJ. Rorden and colleagues presented one stimulus in each visual field of right parietal patients and found patients reported the ipsilesional stimulus preceding the contralesional stimulus unless the latter was presented at least 200 ms earlier (Rorden, Mattingley, Karnath, & Driver, 1997). Sinnett and colleagues presented one shape in each hemifield of right parietal patients and found that the contralesional stimulus had to be presented ~200 ms before the ipsilesional stimulus in order for patients to identify them correctly with equal frequency (Sinnett, Juncadella, Rafal, Azanon, & Soto-Faraco, 2007). Baylis and colleagues asked patients with either left or right parietal damage to report which of two stimuli was the second to appear, and found that a temporal lead of ~ 200 ms was necessary for the contralesional stimulus to be reported as frequently as the ipsilesional stimulus, regardless of the lesion side.

A limitation of some of the earlier studies is that they are confounded by response bias (Robertson, Mattingley, Rorden, & Driver, 1998; Rorden et al., 1997). Patients might simply have preferred to report the stimulus on their "good" side as first when they were uncertain of the temporal order of stimuli: it is well established that parietal patients show strong biases to respond to stimuli on the ipsilesional side (J Driver, 1998). An orthogonal design reduces this confound by asking subjects not to report the side (left vs. right) of the first stimulus, but to report a feature (color, orientation) of the stimulus they perceived first. In addition, if half of the subjects are asked to report such feature for the stimulus they perceived second, the difference between the temporal measures obtained through these subjects and those required to "report feature of first stimulus" provides us with an estimate of response bias as well as an estimate of prior-entry from which

response bias has been removed (Shore et al., 2001). When an orthogonal design was used to control for response bias (Sinnett et al., 2007), and subjects were asked to report a feature of the second stimulus (G. C. Baylis, Simon, Baylis, & Rorden, 2002), TOJ deficits were still observed in patients. Thus even though response biases exist, when they are accounted for and removed, it still seems that both left and right parietal lesions affect TOJ judgments where contralesional visual stimuli appear later than ipsilesional stimuli.

1.4 How attention could affect TOJ: mechanism(s) of prior-entry

The model originally suggested by Schneider and Bavelier provides an interesting starting point for the prior-entry effect (Schneider & Bavelier, 2003). A modified version of their model is proposed by Spence and Parise (Spence & Parise, 2010) in which attention could act at different levels:

1) Attention can cause sensory facilitation at the cued location.

2) Attention might accelerate the transmission of one stimulus relative to the other.

3) Attention can act at the decision level, altering criteria within the decision process.

Points #1 and #2 are based on the same mechanism at the algorithmic level: they both propose that attention causes the attended stimulus to arrive earlier to the comparator (decision-mechanism). However, this notion is not supported by

physiological findings. Although attention increases the gain of neuronal responses in the visual cortex (Reynolds, Pasternak, & Desimone, 2000; Treue & Maunsell, 1999), Lee and colleagues found that directing attention (or shifting attention away), has little effect on the latency of neuronal signals (~1 ms decrease in latency for either 100% or 25% contrast stimuli) (Lee et al., 2007). In another study, Sundberg and colleagues found <1.5 ms of latency changes due to attention at the highest contrast level that they tested (Sundberg, Mitchell, Gawne, & Reynolds, 2012). Similarly Bisley and colleagues found that allocation of attention had no effect on response latencies in LIP (Bisley, Krishna, & Goldberg, 2004). Thus latency differences due to attention, are of extremely small magnitude and cannot explain the large attention effects in TOJ (60 ms for exogenous cues, 17 ms for endogenous cues) (Shore et al., 2001).

Point #3 could serve as a more plausible explanation for the effects of attention. The decision mechanism could be influenced through a shift in criterion. A prevailing model for decisions is that evidence is accumulated as sensory information arrives and a response is triggered when accumulated evidence for one option or another crosses a bound (Luce, 1986; Ratcliff, 1978; Smith, 1990). Attention could either change the bound level (i.e., criterion) for either of the choices or act through shifting the starting point of the "race-to-bound". The same could be proposed for the timing (TOJ) deficits in the parietal patients: a criterion change heavily shifted towards the ipsilesional stimulus would lead to a temporal advantage for these stimuli.

1.5 Phase Discrimination Study

In the first study, we looked at the temporal limits of phase discrimination across the visual field (Aghdaee & Cavanagh, 2007). When two flickering dots are close enough, their relative phase can be judged based on the low-level motion signal between them. However as they become farther apart, the contribution of low-level motion decreases, and relative phase judgments rely on the temporal individuation of light and dark phases of each dot. If individual phases of each flickering dot cannot be accessed, the relative timing between them is lost, and no linking of their phase across the space is possible, making relative phase judgments impossible. At the farthest separation between the two dots, we investigated the highest rate at which individuation can still be maintained, also known as Gestalt flicker fusion (Van-deGrind, Grüsser, & Lunkenheimer, 1973). This rate has been proposed as the "temporal resolution of attention": beyond this rate, one can easily distinguish a flickering dot from an isoluminant dot, but one cannot discern the onset and offset of each dot, a property attributed to temporal properties of attention (Battelli et al., 2001; Verstraten, Cavanagh, & Labianca, 2000). We measured this individuation rate as a function of inter-dot separation at two different eccentricities (4° vs. 14°), and upper vs. lower visual field. We found that the threshold for phase judgments at the largest inter-dot separation (where there is little contribution of low-level motion) decreased by ~30% (11.4 vs. 8.9 Hz) with increased eccentricity (4° vs. 14°). In addition, we found no difference between the thresholds for the upper and lower visual fields. These characteristics of temporal attention are markedly different from those of spatial attention. The spatial resolution of

attention (minimum spacing between items for them to be individuated) is noticeably finer in the lower visual field than the upper field (17-50% advantage for items in the lower visual field (Intriligator & Cavanagh, 2001)), in contrast to what we found for temporal attention. The advantage of foveal presentation is even more pronounced for spatial individuation compared to temporal individuation: while we found a 30% advantage for more foveal stimuli, Intriligator and colleagues found an advantage of almost 300% over a similar range of eccentricities (Intriligator & Cavanagh, 2001).

We conclude that temporal and spatial individuation of visual items have very different properties across the visual field. Assuming individuation is mediated through attention, the umbrella term "attention" exhibits different properties, at least in the space and time domain, with presumably different underlying circuits. These observations underscore the necessity of having an operational definition of attention every time it is used, with particular emphasis on which aspect of attention (feature, space, time) is under study.

1.6 TOJ Study

In the first study, we looked at phase judgments of flickering dots, a consequence of onset/offset judgments across the visual field. In the second study we directly studied onset judgments in an animal model. We trained two monkeys on a TOJ task and looked for neural correlates of such judgments while the animals were engaged in the task. We recorded from single neurons in the lateral intraparietal area (LIP) while the animal

reported the perceived temporal order of two visual stimuli, presented with variable stimulus onset asynchronies (SOAs) in between. Unbeknownst to the monkey, each session also included trials in which the stimuli were presented simultaneously (SOA=0). On these trials, there was no bottom-up information to guide the animal's perceptual choice. We then looked at the neural activity based on whether the animal reported the stimulus in the receptive field (RF) as appearing first or second. We found that LIP neurons show differential activity based on the animal's perceptual report: when the animal reports the stimulus in RF as appearing first, the cells show an increased level of activity compared to when the animal reported the same stimulus as appearing second. This differential activity was most reliable in the tonic period of the response (~100 ms after stimulus onset). However, no difference in visual response latencies was observed between the different perceptual choices.

In summary, we found a neural correlate of temporal order judgments in the parietal lobe. Neuropsychological and imaging studies had suggested the involvement of the parietal cortex in TOJ tasks; neurophysiological studies had also suggested a role for parietal neurons in coding *elapsed* time (Leon & Shadlen, 2003). However, to our knowledge our study is the first to examine the involvement of parietal neurons in encoding *relative* timing. We conclude that through different computations, LIP neurons can encode different aspects of timing judgments.

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Chapter 2

Temporal limits of long-range phase discrimination

2.1 Abstract

When two flickering sources are far enough apart to avoid low-level motion signals, phase judgment relies on the temporal individuation of the light and dark phases of each source. The highest rate at which the individuation can be maintained has been referred to as Gestalt flicker fusion (Van-deGrind et al., 1973) and this has been taken as a measure of the temporal resolution of attention (Battelli et al., 2001; Verstraten et al., 2000). Here we examine the variation of the temporal resolution of attention across the visual field using phase judgments of widely spaced pairs of flickering dots presented either in the upper or lower visual field and at either 4° or 14° eccentricity. We varied inter-dot separation to determine the spacing at which phase discriminations are no longer facilitated by low-level motion signals. Our data for these long-range phase judgments showed that temporal resolution decreases only slightly with increased distance from center of gaze (decrease from 11.4 to 8.9 Hz between 4° to 14°), and does not differ between upper and lower visual fields. We conclude that the variation of the temporal limits of visual attention across the visual field differs markedly from that of the spatial resolution of attention.

2.2 Introduction

Individuation of objects in the world is essential for selecting items for further analyses. In the spatial domain, individuation refers to the ability to select an item independently of its neighbors in order to access the properties—location, color, identity—that belong to it alone. The resolution of spatial selection can be easily demonstrated in a "counting" task as first noted by Landolt in 1891. He reported that bars spaced more closely than 5 arc min of visual angle could be seen, but not counted even when looking right at them: "You get to a point where you can no longer count them at all, even though they remain perfectly and distinctly visible." (Landolt, 1891). If the observer fixates and the bars are presented outside the fovea, the demonstration is even more dramatic as bars spaced by even 1° of visual angle (at 3° eccentricity) cannot be counted one by one (Intriligator & Cavanagh, 2001).

He and colleagues proposed that spatial individuation relied on attentional mechanisms and that its limit served as a measure of the resolution of spatial attention (He, Cavanagh, & Intriligator, 1996, 1997). For example, if the spacing of bars in a grating is finer than this individuation limit but not finer than the limit of visual acuity, observers can see the bars (and differentiate the grating from a uniform field and report its orientation) even though the bars cannot be counted. Thus, in this view, the spatial resolution of attentional selection is far worse than the spatial resolution of vision. Previous studies have shown that the spatial resolution of visual selection is not homogenous across the visual field, dropping sharply with increasing distance from the center of gaze (Intriligator & Cavanagh, 2001). In addition to the inhomogeneity due to

eccentricity, the spatial resolution of attentional selection is coarser in the upper visual field compared to the lower visual field (He et al., 1996; Intriligator & Cavanagh, 2001).

The same concept of individuation in space is also applicable to time. When a white disc is turned on and off on a gray background at a temporal rate of up to 7–10 Hz, the light appears to alternate between "on" and "off" states and observers are able to individuate successive states of light, leading to the experience of steady light–dark alternation. Above this rate, so-called the Gestalt flicker fusion rate, the light is experienced as a constant flicker without individual light and dark states (Grüsser & Landis, 1991; Van-deGrind et al., 1973). The temporal limitation of 7–10 Hz is also found in several other tasks. Battelli and colleagues reported temporal rates of 8–10 Hz as thresholds when subjects had to discriminate between apparent motion and synchronous presentation of stimuli (Battelli et al., 2001). Verstraten and colleagues showed that the maximum rate at which observers could attentively track a bi-stable moving display or report the direction of unambiguous apparent motion or track a continuously moving target was around 4–8 Hz (Verstraten et al., 2000). Temporal rates for phase discrimination of flickering lights show similar temporal limitations (He, Intriligator, Verstraten, & Cavanagh, 1998; He & MacLeod, 1993; Rogers-Ramachandran & Ramachandran, 1998). In addition, the temporal rate at or above which direction discrimination of cyclopean motion fails is 8 Hz (Patterson, Ricker, McGary, & Rose, 1992). These and other data have led several authors to propose both a slow and a fast mechanism for detecting phase differences (Forte, Hogben, & Ross, 1999; Rogers-Ramachandran & Ramachandran, 1998; Victor & Conte, 2002) where the fast mechanism can only work over short distances whereas the slow mechanism can operate

over very large distances. The temporal limit of the slow mechanism has been linked to the temporal resolution of attention where the individuation of the light and dark phases of the flicker is assumed to be mediated by visual attention (Battelli et al., 2003; Verstraten et al., 2000). Note that this temporal limit is much lower than the temporal resolution of vision, which is around 30–50 Hz (Andrews, White, Binder, & Purves, 1996; Rovamo & Raninen, 1984). Thus, homologous to the spatial resolution of attention, the temporal resolution of visual attention is much coarser than the temporal resolution of vision.

The origin of the variations of spatial resolution of attention across the visual field may arise from the properties of the cortices where attention operates. The mapping from retina to cortex (the cortical magnification factor) has different organization for different visual cortices (Gattass, Gross, & Sandell, 1981; Gattass, Sousa, & Gross, 1988). The underlying assumption is that an "attentive field" has a constant size on the visual cortex on which it operates, so that the scaling of the attentional field with eccentricity reflects the cortical magnification factor of that particular cortex. Parietal areas are often implicated in the control of spatial attention (Culham et al., 1998; Posner, Walker, Friedrich, & Rafal, 1987; Posner, Walker, Friedrich, & Rafal, 1984). Parietal areas receive more input from the lower visual field compared to the upper visual field (Maunsell & Newsome, 1987), a factor that may contribute to the finer resolution of spatial attention in the lower visual field.

In contrast, there is no corresponding temporal cortical magnification factor yet identified. The flicker fusion rate does not vary across the visual field either as a function of eccentricity or as a function of visual field (upper vs. lower) (Rovamo & Raninen,

1984). This suggests that the temporal resolution of low-level (visual) mechanisms is relatively homogeneous across the visual field. Will high-level, attention-based temporal mechanisms follow the pattern of flicker fusion or that of spatial attention? If temporal and spatial attention show similar limits across the visual field, it would suggest that spatial and temporal attention rely on a common resource.

We used phase judgments between two flickering dots to evaluate the temporal resolution at two eccentricities separately in the upper and lower visual fields. When two flickering discs are close to each other, they may both fall inside the receptive field of a directionally selective unit in primary visual cortex. In this case, a strong motion percept accompanies even small phase shifts between the two flickering dots and the rates that support discrimination between in-phase and out-of-phase flicker approach flicker fusion rates (Anstis, 1980; Boulton & Baker, 1993). As the spacing between the discs increases, the contribution of low-level motion signals diminishes, and in the limit, the phase discrimination relies solely on high-level signals (including high-level motion if elicited). In this case, observers can perform the task only at much lower temporal rates (Anstis, 1980; Battelli et al., 2001). It has been shown that with large displacements between the stimuli, attentional mechanisms are necessary, requiring the detection of appearances and disappearances and combining these events, which consequently leads to motion perception (Dick, Ullman, & Sagi, 1987). We expect that as we increase the inter-dot spacing, phase judgments will deteriorate up to a particular point (representing the limit of low-level motion) and stay relatively constant for spacings beyond that point.

The properties of slow and fast mechanisms for temporal phase judgment were studied by Forte and Colleagues (Forte et al., 1999). They presented a regular array of

flickering Gaussian spots where the spots in one quadrant were out-of-phase with those in the other quadrants. Their results showed that the fast mechanism could operate only when the separation between spots of different phase was 0.4° or less. The array used by these investigators covered all quadrants and the separation between the differing phase spots always lay along the horizontal and vertical meridian stretching from the fovea to about 5° eccentricity. As a result, their data offer no information about the effects of eccentricity or visual field on the temporal limits of the slow mechanism. Victor and Conte also reported that the fast phase mechanism is severely impaired by separation between the stimuli (Victor & Conte, 2002). However, they did not evaluate the effects of eccentricity or visual field either.

The aim of this study was to look at rate thresholds of phase discrimination for pairs of flickering discs to see whether the thresholds change when stimuli are presented at different eccentricities and across (upper vs. lower) visual fields. The spacing between the discs was varied, and the threshold at which observers could report the relative phase of the flickering discs at 75% accuracy was considered as the threshold at each inter-disc spacing. As discussed above, presenting the stimuli at different inter-disc spacings allows us to separate the contribution of low-level and high-level signals in the task. In our study we obtained thresholds for stimuli presented at two different eccentricities of 4° and 14° and in each of the four quadrants (upper and lower, left and right).

2.3 Obtaining thresholds at 4° and 14° eccentricity

2.3.1 Methods

2.3.1.1 Observers

Four observers (two females and two males) ranging in age from 26 to 31 years participated in this experiment. All observers had normal or corrected-to-normal visual acuity. One of the observers was the author (SMA) and three others were experienced observers naïve to the purposes of the experiment.

2.3.1.2 Apparatus

The stimuli and the psychophysical experiment were programmed in MATLAB, using the Psychophysics Toolbox extensions (Brainard, 1997; Pelli, 1997). Images were displayed on an Apple color monitor, 800H × 600V pixel resolution (120 Hz refresh rate) controlled by a Macintosh G4 computer. Observers were placed in a dark room and viewed displays binocularly while their heads were fixed on a chin and forehead rest. The viewing distance was 44 cm.

2.3.1.3 Stimuli

The fixation point was a black dot with a diameter of 0.22° (0.06 cd/m^2). Stimuli were a pair of white circular discs (86.4 cd/m^2) presented on a uniform gray background (20.4 cd/m^2). The stimulus pair was presented either at 4° or 14° eccentricity, each subtending 1° or 2.25°, respectively. The size of the discs at the more eccentric location was increased using M-scaling to account for cortical magnification. At each eccentricity both discs were located on the circumference of an imaginary circle with a radius of the

corresponding eccentricity and with equal distance from the 45° or 135° lines drawn from the fixation point.

The center-to-center separation between the discs was set at six different levels for each eccentricity. The inter-disc spacings used for the 4° eccentricity included 1.25°, 1.75°, 2.4°, 3°, 3.75° and 4.5°. For the 14° eccentricity, the spacings we used included 2.81°, 3.94°, 5.4°, 6.75°, 11.25° and 15.75°. The separation between the discs at 14° was increased to match the eccentricity and larger size of discs. The spacing between the discs always insured that both remained in the same quadrant.

Two sets of temporal frequencies at which the discs flickered were used: at both eccentricities, for the three smaller inter-disc separations, the frequencies tested were 6, 7.5, 8.5, 10, 12, 15, 20 and 30 Hz. For the three larger inter-disc separations, the frequencies tested were 5, 6, 7.5, 8.5, 10, 12, 15 and 20 Hz.

2.3.1.4 Procedure

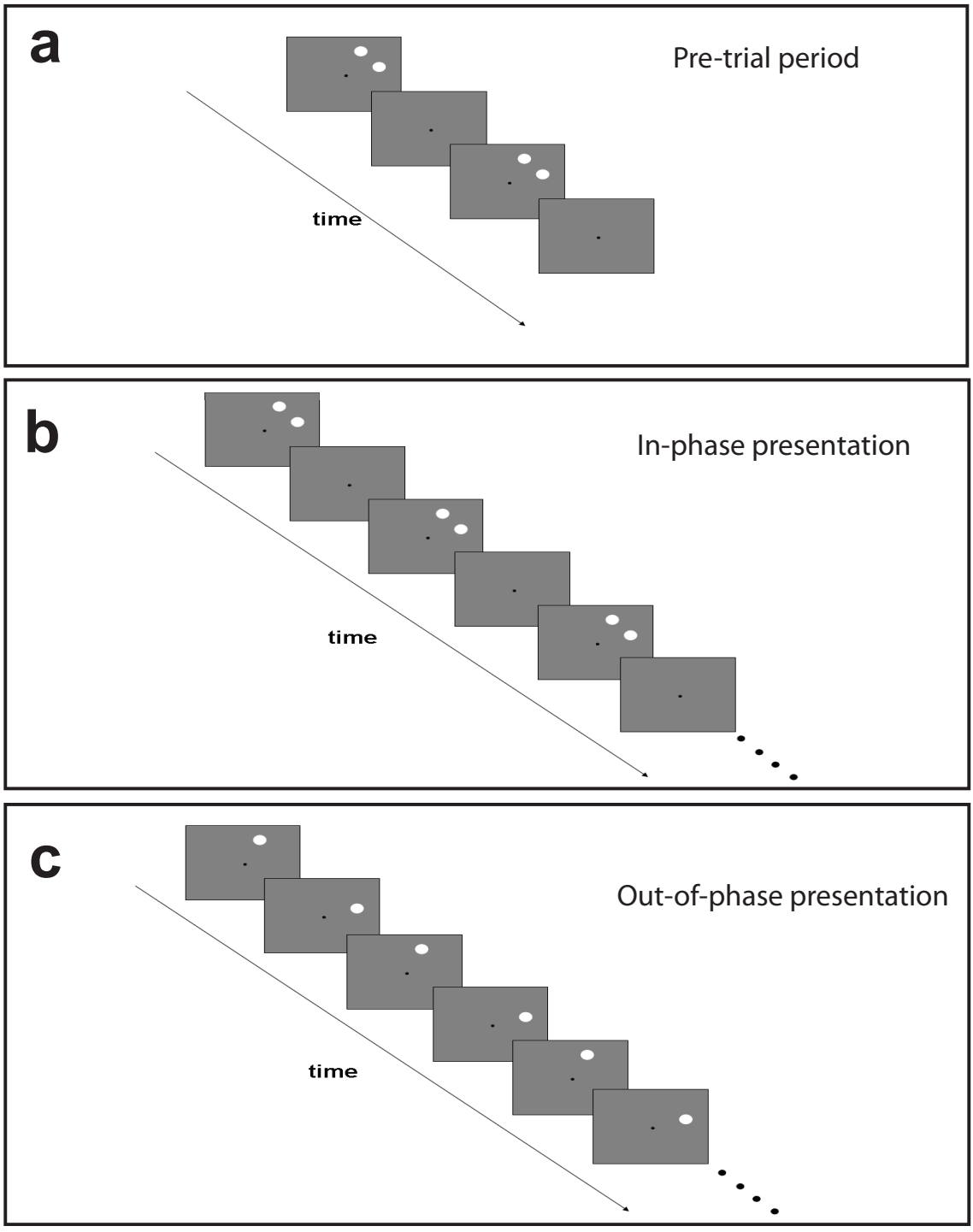
Before each trial, there was a pre-trial phase of 33 ms, during which both discs were flashed simultaneously for two cycles (Figure 1). This was done in order to prevent observers making their phase judgments based on the cue in the first frame (i.e., seeing one disc in the out-of-phase presentation or two discs in the in-phase presentation).

During each trial, the two discs were presented flickering either in-phase or 180° out-of-phase (i.e., both discs appearing at the same time or one appearing when the other one disappeared). The relative phase of the two discs was randomly assigned and the observer's task was to report their relative phase using either of a pair of keys on the computer keyboard. Exposure time for each trial was set to 500 ms. The next trial proceeded after a 1 sec inter-trial interval. In each trial the inter-disc separation, the

quadrant in which the stimulus appeared and the flickering rate of discs were randomly assigned at the beginning of each block. Each block consisted of 384 trials (stimulus type (2) × visual quadrant (4) × spacing (6) × temporal frequency (8)), and each observer performed 10 blocks.

Figure 1. The experimental paradigm. Observer's task was to report whether the flickering dots appeared in-phase or out-of-phase. **(a)** The pre-trial condition. During this period, both stimuli flashed for two cycles. The pre-trial condition preceded both the in-phase and the out-of-phase presentation of the stimuli**. (b)** In-phase presentation of the stimuli. **(c)** Out-of-phase presentation of the stimuli. The presentation time was 500 ms.

Figure 1 (Continued)



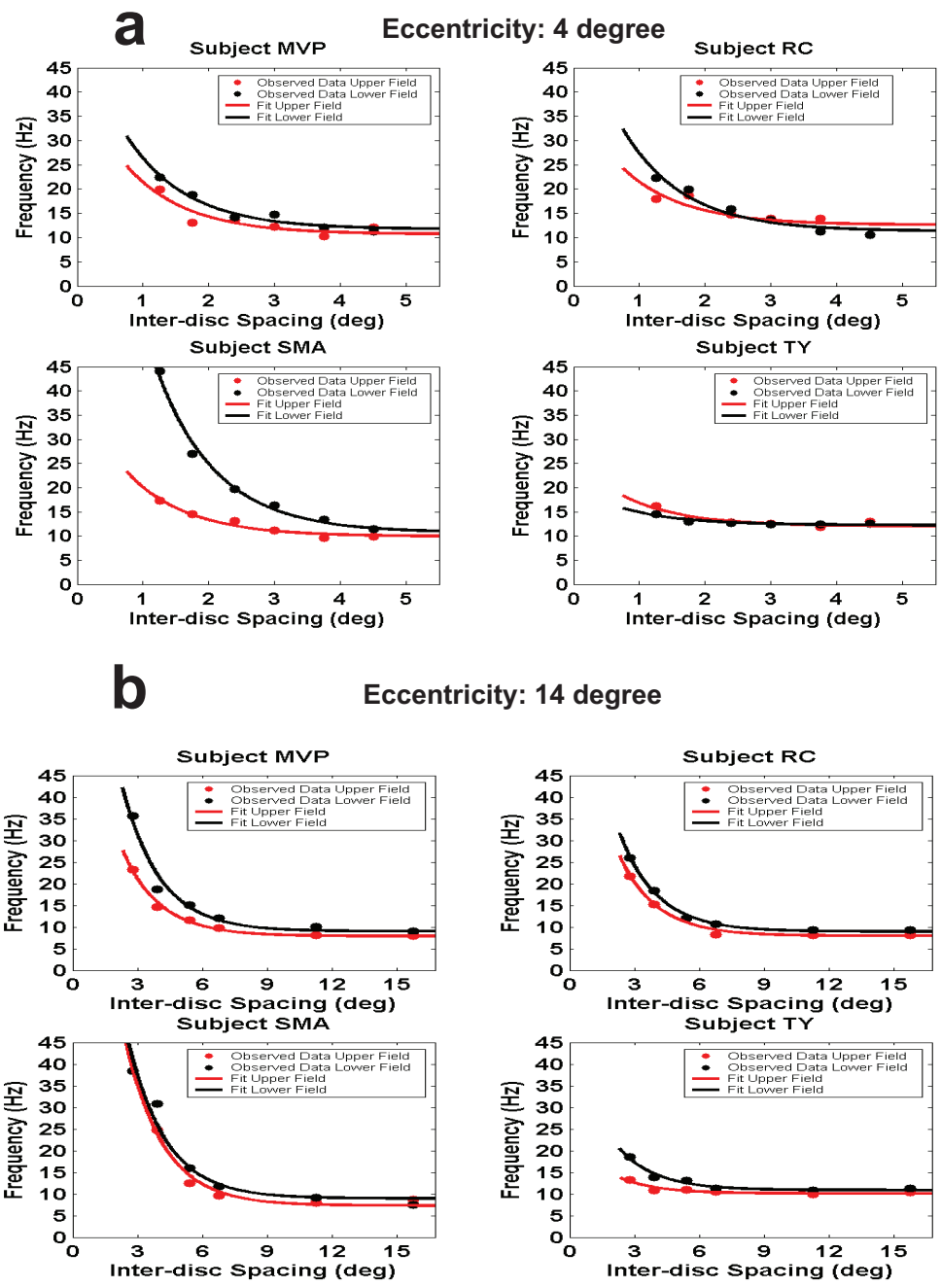
2.4 Results

The phase discrimination threshold was determined for each inter-disc separation, eccentricity and visual field, separately for each observer. No difference was observed between any observer's performance in the left and right hemifield and thus the data for the left and right hemifields were pooled. The data were fit with a Probit function and the temporal rate at which observers could discriminate in-phase vs. out-of-phase presentation of the flickering discs with 75% accuracy was taken as the discrimination threshold at that particular inter-disc separation.

After deriving the thresholds for each inter-disc separation, these values were plotted against inter-disc spacings (Figure 2a-b). The threshold vs. inter-disc spacing data showed an exponential drop in the frequency limit as a function of spacing as the low-level motion contribution decreased. In each case, the frequency limit settled to a steady value that indicated the performance when no low-level motion responses contributed. To recover this asymptotic value for the long-range phase judgments, each subject's data was fit with an exponential function ($y = a \cdot \exp(-b \cdot x) + c$) for each eccentricity and upper vs. lower visual field. At each eccentricity, we fitted all eight curves (four subjects × two visual fields) simultaneously, fitting one decay rate (b parameter) for all curves and recovering a separate a (starting value) and c (the asymptotic limit) for each curve. The asymptote of the fitted model was the temporal frequency at which each observer could perform the phase discrimination task with 75% (or higher) accuracy, independently of low-level motion signals.

Figure 2. **(a)** Temporal frequency thresholds for phase judgments as a function of inter-disc separation at 4° eccentricity. Data for each subject is shown separately. Each dot represents the temporal frequency that allowed 75% correct performance at that particular inter-disc separation. The curves are the exponential fits to the data. Red and black colors show data corresponding to upper and lower visual fields, respectively. **(b)** Temporal frequency thresholds for phase judgments as a function of inter-disc separation at 14° eccentricity. Same format as in **a**. **(c)** Long-range phase discrimination thresholds at 4° and 14° eccentricities. Data for each subject are shown separately. Each threshold is the asymptote value of the exponential fit to each threshold vs. frequency function (2a and 2b). Error bars represent ±1 standard error of the fit parameter *c*. Red and black colors show data corresponding to upper and lower visual fields, respectively.

Figure 2 (Continued)



c

Figure 2 (Continued)

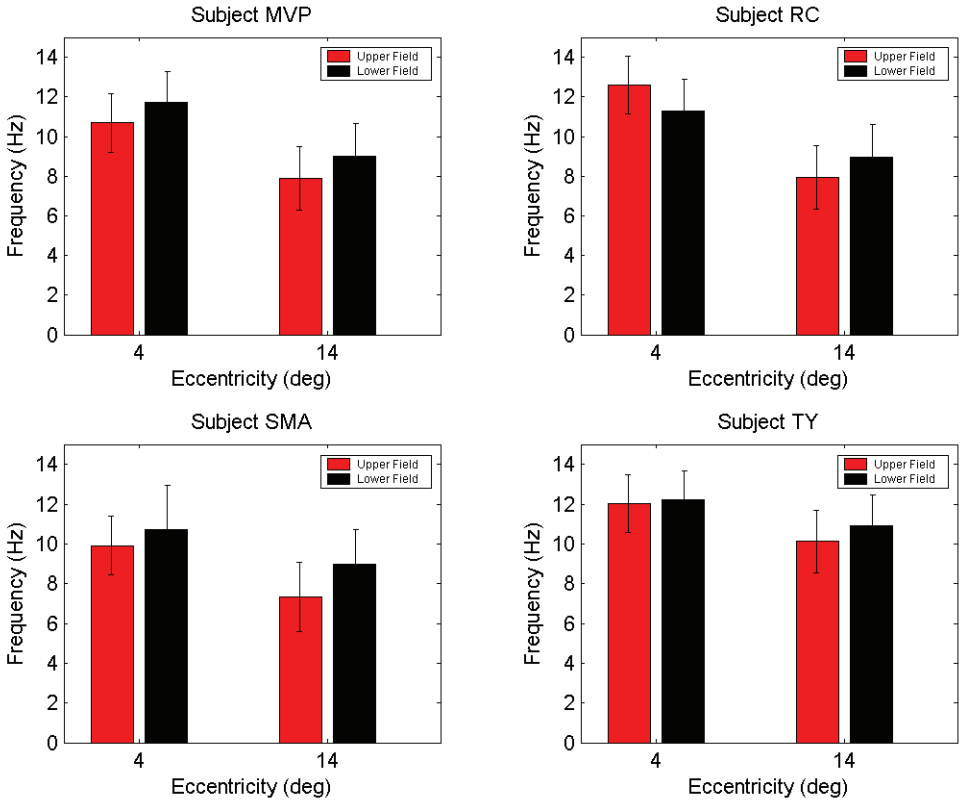


Figure 2c compares the asymptotic values (long-range phase judgment thresholds) obtained for each eccentricity and visual field in each individual subject. To study the effect of eccentricity and visual field across all subjects, a two-way ANOVA with repeated measures [eccentricity (4° vs. 14°) and visual field (upper vs. lower)] was performed on the long-range phase thresholds (i.e., the asymptote value for each curve in Figure 2a-b). A significant effect was found for the effect of eccentricity ($F(1, 3) = 38.43$, $P < 0.01$). No significant effect was found for the effect of visual field ($F(1, 3) = 4.67$, $P = 0.12$, *NS*) nor for the interaction between eccentricity and visual field ($F(1, 3) = 4.01$, $P = 0.14$ *NS*). As shown in Figure 2c the eccentricity effect did not show significance in the data of individual subjects and the effect became significant only in the group data.

We also compared the cut-off point for the contribution of low-level mechanisms in the drop-off of performance as dot spacing increased. We took the $1/e$ value for this cut-off spatial separation (spacing = $1/b$) for the two different eccentricities. We expect this value to be larger at the greater eccentricity as the receptive field size for low-level motion detectors increases with eccentricity, as indicated by physiological measures (Hubel & Wiesel, 1974) and by D_{max} measures (Baker & Braddick, 1985). The $1/e$ range of the low-level mechanisms suggested from our data was about 0.91° at 4° and 1.75° at 14° (Explained further in Discussion).

Finally, we ran a control to examine the effect of the pre-trial frames where both dots were present simultaneously. These were present to mask any obvious cues to phase in the initial test frame. Specifically, the first frame had two dots in the in-phase trials, but only one in the out-of-phase trials. The pre-trial frames may not have been effective

or may have provided other cues to phase. Also we did not, in the main experiment, add any trailing frames to mask the offset cues to phase. Control data were collected in three conditions: the original condition, a condition where there were no pre-trial frames and a condition where there were both a pre-trial and a post-trial phase (the post-trial phase was identical to the pre-trial phase, except that it followed the stimulus presentation). We tested only one spatial separation (asymptotic separation) and one temporal rate (threshold rate) and looked at percent correct to see whether there was any effect of the presence of the pre- and post-trial phase. Data was collected from two subjects who had previously participated in the original experiment. A two-way ANOVA analysis [visual field (upper vs. lower) and presentation condition (only pre-trial vs. no pre-trial vs. both pre-trial and post-trial)] was performed. No effect was found for presentation condition ($F(2, 11) = 0.18$; P-value = 0.84). Thus, while we inserted the pre-trial phase as a cautionary measure, their presence apparently neither helped nor hindered observers.

2.5 Discussion

Our results show that, as measured by long-range phase judgments, the temporal limits of visual selection do not differ between the upper and lower visual fields, and decrease only moderately with eccentricity. We claim that the temporal limits we have measured reflect the temporal resolution of attention. This claim is based on the assumption that attention is required to individuate the phases of the flickering stimuli: without individuation (via attention), the flickering stimuli cannot be broken down into

discrete phases and, in the absence of low-level motion cues, it is no longer possible to compare the instantaneous phases of the two flickering dots.

Our data show that the temporal resolution of attention shows no significant effect of visual field, while spatial resolution of attention shows a noticeable advantage for the lower field presentation (between 17% and 50% advantage for the lower field, (Intriligator & Cavanagh, 2001)). In addition, even though both spatial and temporal resolution of attention are better near the fovea than in the periphery, the magnitude of the change is very different: the resolution in spatial attention increases by 288%, from 0.50 targets/° at 15° eccentricity to 1.94 targets/° at 3.5° eccentricity (tangential stepping task, computed as 75% threshold for single selection step, average of upper and lower fields (Intriligator & Cavanagh, 2001)) whereas the temporal resolution of attention improves by only 28%, from 8.9 to 11.4 Hz, between 14° and 4°.

We should emphasize that the task we used in our study is as much as possible, the temporal equivalent to that used for studying spatial resolution of attention (Intriligator & Cavanagh, 2001) and thus comparison of spatial and temporal limits of attention from the two tasks are meaningful. For studying the spatial limitations of attention (Intriligator & Cavanagh, 2001) an array of dots was presented in the periphery and one dot was cued. Following computer commands, subjects stepped mentally back and forth from dot to dot only using attention (keeping fixation) until a probe was presented and subjects reported whether the probe was on the dot they had stepped to. The task could be performed only if attention could (spatially) individuate the items, allowing attention to move from one dot to the next. For item-to-item spacings closer than the resolution of spatial attention, targets could not be spatially individuated and

tracking was not possible. For studying the resolution of temporal attention, the equivalent question is posed for spacing of items in time rather than space. If items were presented too closely spaced in time to be individuated, tasks that require access to the individual dot appearances would fail. To test temporal resolution at different eccentricities, we chose the phase judgment task where two dots flickered either in- or out-of-phase. Discriminating the relative phase of the flickering stimuli is possible only if each light and dark phase of a flickering dot can be accessed individually. If not, the two dot locations are both seen as undifferentiated flicker, the relative timing between the dots is lost, and no cross-location pairing can be made that supports the phase judgment. We believe this approach is equivalent to the spatial tests. In the spatial case, the question asked was whether the closely spaced adjacent dots could be individuated and thus allowed stepping from one to the other. In the temporal case, we asked whether dot flashes, closely spaced in time, were sufficiently individuated from the following flashes at the same location to support a comparison of phase between the two locations. In either the spatial or temporal cases, if the locations or moments were not individuated, the stepping or phase comparison failed.

The temporal threshold levels obtained in our study are in the same range of those reported previously. Gestalt flicker fusion, the temporal rate at which observers can individuate successive states of light, is around 7–10 Hz (Grüsser & Landis, 1991; Van-deGrind et al., 1973). Above this rate, there is no access to the individual state of each "on" and "off" event. As a result, the percept changes: the spot of light seems to be flickering continuously with no discrete appearances and disappearances. In a study where subjects had to discriminate between apparent motion and synchronous

presentation of stimuli, similar thresholds were obtained (Battelli et al., 2001). Verstraten and colleagues showed that above the rate of 4–8 Hz, observers could not attentively track a bi-stable moving display, neither could they report the direction of unambiguous apparent motion nor track a continuously moving target (Verstraten et al., 2000). Phase judgments for widely spaced items (Forte et al., 1999; Victor & Conte, 2002) and discrimination of flickering lights (He et al., 1998; He & MacLeod, 1993; Rogers-Ramachandran & Ramachandran, 1998) and direction discrimination of cyclopean motion (Patterson et al., 1992) all show the similar 7–10 Hz limitation on temporal selection. It has been suggested that this temporal limitation is imposed by attentional mechanisms (Forte et al., 1999; Verstraten et al., 2000).

As predicted (see Introduction), when we increased the inter-dot spacing, phase judgments deteriorated up to a particular spacing (representing the limit of low-level motion) and stayed relatively constant beyond that point. The inter-disc separation at which low-level motion drops away and performance relies on high-level signal is similar to the D_{max} measure (O. Braddick, 1974), the maximum displacement of random dot pattern that supports low-level motion perception. D_{max} gives a good measure of the spatial range of low-level motion because the random dot patterns do not offer any obvious large-scale shape to track over distances beyond the limit of low-level motion. In our display, however, only single dots are presented, so that once the limit of low-level contribution is exceeded, motion of the dot can still be seen based on high-level object tracking (O. J. Braddick, 1980; Cavanagh, 1992). We used performance at separations beyond this asymptote to estimate the properties of high-level mechanisms. Over some range, low-level motion may mediate the phase judgment decision, but at larger spacings,

motion may not be seen and phase judgments will be based on perception of simultaneity vs. non-simultaneity. In either case, we assume that the performance reflects the underlying individuation of the "on" and "off" phases of each dot and reveals the temporal limits of visual attention.

As it can be seen in Figure 2a-b, at each eccentricity the threshold rates are highest for the closest spacing between the discs. When discs are close enough, observers can perform the simultaneity judgments based on low-level motion signals between the dots. As the spacing between the discs increases, the contribution of low-level motion signals diminishes, leading to a drop-off in the thresholds. At each eccentricity we also compared the inter-disc spacing beyond which the low-level motion signal between out-of-phase discs is dominated by the high-level signal. We chose the rate that produced a drop to 1/*e* of the maximum value as our measure of this cut-off point (given by the inverse of the exponential decay rate, *b*, in the function that we fit to the data). This 1/*e* inter-disc spacing (1/*b*) is 0.91° at 4° eccentricity vs. 1.75° at 14° eccentricity. Thus, with increased eccentricity, the inter-disc spacing at which high-level motion signals dominate low-level motion signals increases. This is in accord with studies which report an increase in D_{max}, the limit of the low-level motion system, with eccentricity (Baker & Braddick, 1985), where they found an increase in D_{max} from 0.83° at 4° eccentricity to 1.66° at 10° eccentricity.

The parietal cortex has been the candidate cortical region for visual spatial selection (Corbetta, Shulman, Miezin, & Petersen, 1995; J. Driver & Mattingley, 1998; Posner et al., 1987). Patients' deficits are not restricted to spatial tasks and they also exhibit problems in the time domain. Husain and colleagues showed that parietal patients

suffer from timing deficits, as their attentional blink period is three times longer than controls (Husain et al., 1997). However, neuropsychological data suggest that there are differences in terms of cortical regions for spatial and temporal selection. In contrast to neglect syndrome, where the spatial deficits in attention only affect the contra-lateral visual hemifield, patients with right parietal damage have slower temporal selection rates in both left and right visual fields (Battelli et al., 2001).

In conclusion, we found that *temporal* resolution of attention as measured by long-range phase judgments, shows a small decrease with eccentricity, and no upper vs. lower visual field difference. In contrast, the *spatial* resolution of attention shows both a foveal and lower visual field advantage. These results suggest that the advantages seen for foveal and lower field presentation cannot be attributed to general attentional factors; they are specific to spatial attention. This also suggests that spatial and temporal properties of visual attention are mediated by different cortical networks.

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Chapter 3

Temporal order judgment in lateral intraparietal cortex

3.1 Introduction

Temporal Order Judgment (TOJ) refers to the task of reporting which one of a pair of stimuli was perceived first. The topic was brought to the attention of scientists in the early 19th century from the field of astronomy, where astronomers had to estimate the transit time of stars using the ear-and-eye method: for the distance *x* they used reticle lines on the telescope eye-piece and for the time *t* they would listen to beats of a clock, and then matched which beat of the clock corresponded to the instance the star passed a particular line on the eye-piece, making a *temporal order judgment* between the visual and the auditory signals. Astronomers realized that there could be up to one-second difference between observations of different individuals. These errors in reporting the relative timing of visual vs. auditory events, as well as the inter-subject differences led Gustav Fechner and Wilhelm Wundt to launch the fields of psychophysics and experimental psychology (Boring, 1929; Gregory, 2004; Hergenhahn, 2004). More detailed psychological studies followed on the reporting of temporal order of sensory events, a.k.a. *Temporal Order Judgment* (TOJ), as well as the errors involved in this task.

Although the initial observations of errors in judging temporal order were made between visual and auditory stimuli, the study of TOJ has mostly focused within a sensory modality. In the case of vision, it is well-known that the physical order of visual events may not correspond to that of their perceived order: when two visual stimuli are presented in close temporal proximity, they can be perceived simultaneously or even with reversed order, especially when the inter-stimulus interval is very brief. In addition,

simultaneous stimuli can also be perceived as temporally successive events (Sternberg & Knoll, 1973; Ulrich, 1987).

A variety of behavioral studies have provided clues about the properties of TOJ and highlighted some of the visual areas involved. One approach has been to compare order judgment when both stimuli are presented to one eye (monoptic) versus when the stimuli are presented separately in the two eyes (dichotic). The threshold (asynchrony at which the subject could correctly report the temporal order on 75% of trials) for order judgment is lower when stimuli are presented monoptically (Westheimer, 1983; Westheimer & McKee, 1977), suggesting involvement of brain areas with monocular neurons in TOJ. Observers also have a bias of reporting foveal stimuli to appear before peripheral stimuli (Westheimer, 1983). However, in both the aforementioned studies the two stimuli were in extremely close proximity to each other, with only arc minutes of separation. Temporal order judgments at this scale may be best subserved by neurons with small receptive fields in early visual areas. In addition two successive stimuli in close spatial proximity could produce a dominant low-level motion signal that could allow observers to perform the task based on motion cues rather than order judgment per se (Braitenberg, 1974).

Localization studies have led to a better understanding of visual areas governing temporal order judgments. The parietal cortex seems to play a particularly important role. For example, patients with damage to right parietal cortex have a bias to report the stimulus on the contralateral side as appearing later (Rorden et al., 1997). In addition, temporary disruptive techniques demonstrate a causal role of the right parietal lobe in TOJ. For example, applying precisely-timed online transcranial magnetic stimulation

(TMS) to the right, but not left parietal cortex delays detection of a visual target on the contralateral side (Woo et al., 2009). However, not all studies confirm that TOJ effects are mediated through the right (and not left) parietal cortex (G. C. Baylis et al., 2002; Davis et al., 2009). In addition, it is not known whether the involvement of right parietal cortex in TOJ tasks is through the well-documented role of right parietal cortex in temporal attentional processing (Battelli et al., 2001; Battelli et al., 2003), because the stimulus configuration could produce a high-level (attention-based) motion signal (i.e., motion signals for which the Δx and/or Δt are out of the range for low-level motion mechanisms) (Baker & Braddick, 1985; O. Braddick, 1974). As explained later, we designed our experimental paradigm in such a way to reduce possible motion cues from influencing the temporal order judgment.

There are also several lines of physiological evidence pointing to a role for parietal cortex in relative timing. Bisley and colleagues showed that neurons in the lateral intraparietal area (LIP) have an extremely short (mean, 45.2 ms) and precise visual latency: from single unit examples shown in their figure 1, the rise to maximum activity from baseline occured in less than 10 ms (Bisley et al., 2004). In addition they showed that the timing of the response was not affected by an earlier presentation of a task-irrelevant stimulus in the RF (Bisley et al., 2004), suggesting that the spike-time information was very reliable and could subserve timing processes even in the face of distracting visual information. Leon and Shadlen showed that LIP neurons represent elapsed time when the animals had to make eye movements to indicate whether the duration of a test stimulus was shorter or longer than a reference duration (Leon & Shadlen, 2003). However, our experiment focused on *relative* time, which involves

comparing the onset/offset of visual stimuli rather than estimating elapsed time. Finally previous work has shown that, compared to lower visual areas, neural activity in LIP is more aligned with the subjective experience of subjects, rather than the physical aspects of the stimulus (Williams, Elfar, Eskandar, Toth, & Assad, 2003). Thus one might also be able to find a signature of relative-timing perception or decision in LIP even when the low-level evidence is ambiguous, such as when two visual targets appear simultaneously.

To study the neural correlates of temporal order judgment, we trained two macaque monkeys to report the perceived order of two visual stimuli (task explained in detail in next section). We trained the animals until their behavioral performance was stable and then recorded from single neurons in area LIP.

3.2 Methods

3.2.1 Animal Preparation

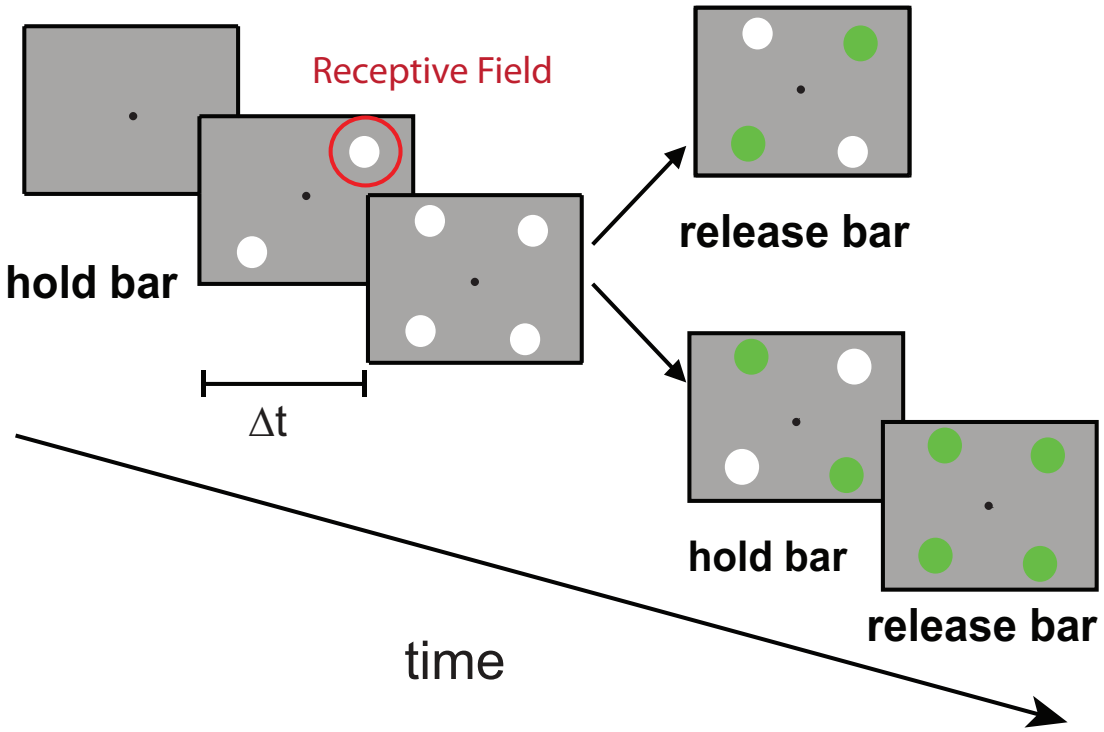
Two adult male rhesus monkeys (*Macaca mulatta*, Monkey E: 13 kg; monkey M: 17 kg) were implanted with a recording chamber, head post and scleral search coil (Robinson, 1963) and used as subjects. All surgical and experimental procedures were in accordance with Harvard Medical School and US National Institutes of Health guidelines. Animals were trained extensively (6-9 months) before collection of the neurophysiological data.

3.2.2 Behavioral Task

The monkeys' task was to make order judgments regarding the onset of visual stimuli presented on a CRT monitor (Figure 3). The experiment was divided into discrete trials of several seconds' length. At the start of each trial, a small spot (0.2-0.4° in diameter, green in monkey E, white in monkey M) was presented on the monitor as a fixation point (FP). The monkey had to direct its gaze to the fixation point and maintain fixation within 1.1-1.3° of the fixation point throughout the trial, or the trial would abort. The animal also initiated hand contact with a touch-sensitive bar. After a variable delay of 300-800 ms, a pair of white circles, (each 0.8-1° in radius, scaled with eccentricity) appeared on the display monitor, followed by another pair of white circles, with a variable amount of time between the onset of each pair. After both pairs of stimuli were presented, one of the two pairs, chosen randomly, turned green (250 and 350 ms after the onset of the second pair for monkey E and M, respectively). If the pair that turned green was the pair that had been presented *first*, the animal had to release the touch bar within 200-650 ms to get a drop of juice. If instead the pair that turned green had been presented *second*, the monkey had to maintain hand contact with the touch bar until the other pair also turned green (650 ms afterwards), when he would release the touch bar to receive a drop of juice. The juice was delivered by a solenoid valve 500 ms after release of the touch bar. Trials were separated by a 1000 ms inter-trial interval.

Figure 3. Behavioral paradigm. The trial starts with the fixation point appearing on the screen. After the monkey fixates his gaze and makes hand contact with the touch-sensitive bar, a pair of white circles appear on the screen, followed by another pair after a variable temporal delay (Stimulus Onset Asynchrony). One of the four circles falls in the receptive field (RF) of the unit. The pair of stimuli with the circle falling in the RF could appear first or second on the monitor, at random (in this figure, the RF-stimulus appears first). Afterwards one of the pairs changes color from white to green. The monkey's task is to make a "match-to first" response using the touch bar: if the pair turning green appeared first, the animal should release the touch bar to receive a juice reward. If the pair turning green appeared second, the animal must maintain his hold on the touch bar until the other pair also turns green, when he should release the touch bar to receive a juice reward.

Figure 3 (Continued)



Vertical and horizontal eye positions were monitored using a scleral search coil system (Riverbend Instruments) and sampled at a rate of 200 Hz. Trials in which the monkey broke fixation before the juice delivery were aborted without reward. Hand contact (through the touch-sensitive bar) was also monitored at 200 Hz, and trials in which the animal released the touch bar prematurely were also aborted without reward.

The time between the onset of the two pairs of stimuli (the stimulus onset asynchrony, or SOA) was varied between 9-92 ms for Monkey M and 9-126 ms for monkey E. The slightly different ranges of SOAs were chosen for the two animals to best encompass the animals' individual operating psychophysical ranges. We used a CRT monitor with a fast refresh rate (120 Hz) to allow for the short SOAs. The SOA was chosen randomly on each trial. In addition, on some trials, the two stimulus pairs were presented simultaneously (SOA=0). Zero SOA trials, which were randomly dispersed among trials with non-zero SOA, had no corresponding correct response. On these trials one pair was randomly assigned as first, and the animal received reward if he made the appropriate touch-bar response. The overall reward received for SOA=0 ms trials was thus ~ 50%. It is plausible that due to the raster presentation of the monitor, spots within a pair were not presented simultaneously where the delay between them would vary depending on the stimulus configuration. However, as seen in the behavioral data in Figure 4, this delay is small compared with 10-90% values of the psychometric function.

The two circles within a given stimulus pair were always presented simultaneously, on the same video frame. The two circles in each stimulus pair were

arrayed equidistant from the fixation point, with the center of each circle and the fixation point describing a straight line. The second pair of stimuli was always arrayed with its axis orthogonal to the axis of the first pair. After each pair of stimuli appeared, they remained on the screen and were not erased until the end of the trial. This was done to reduce the perception of apparent motion induced by the successive presentation of the two pairs of stimuli. One might wonder why a *pair* of circles was used for each stimulus, rather than a single circle. If each stimulus were a single circle, the successive presentation of two circles would lead to a strong percept of motion, starting from the first stimulus and terminating at the second stimulus. If so, the animal could make his temporal judgments solely based on the direction of the perceived motion. In our experiment, the orthogonal configuration of stimulus pair 1 and stimulus pair 2 ensured that apparent motion could not be used as a cue in performing the temporal order judgment, because any apparent motion should appear as a *rotation* of the two pairs around the fixation point, like a wagon wheel. More importantly, the perceived direction of any rotational apparent motion should be *ambiguous* – either clockwise or counterclockwise – and either direction of rotation could be compatible with one or the other stimulus pair appearing first. Thus apparent motion could not provide clues as to the order of stimulus-pair presentation. In fact, subjectively we did not notice any obvious sense of apparent motion given the spatiotemporal parameters of our stimuli.

At the beginning of each trial, the SOA was chosen randomly. For a given $|\Delta t|$ there were two sequences in which the stimuli could be presented: pair A -$|\Delta t|$- pair B and pair B -$|\Delta t|$- pair A. Thus for any temporal asynchrony, there were four possible trial outcomes: pair A/B onset first/second & pair A/B turns green first/second. All four trial

outcomes were interleaved randomly and were equally likely. This was obviously necessary to ensure that the monkeys could not simply cue on the location of the green color change.

An important aspect of this task was that the monkey's percept of temporal order was dissociated from *how* he reported his percept: the order of stimulus-pair presentation was independent of the match vs. non-match contingency. That is, the animal could not determine the correct motor response (release the bar or maintain contact with it) until one pair of stimuli turned green. If a particular temporal order judgment were instead rigorously mapped to a particular motor response, neuronal activity that is recorded during the task could reflect motor planning per se rather than the temporal order judgment (Freedman & Assad, 2011). In addition, the monkey's response does not involve any overt saccadic eye movements to the location of stimuli or pre-designated saccade targets. These last two aspects of the task are especially important given the eye-movement related activity of LIP neurons (Andersen & Buneo, 2002; Snyder, Batista, & Andersen, 1997).

During match trials, if the monkey released the touch bar within the designated 450 ms (200-650 ms after color change), he was rewarded, and the trial would be labeled as *correct.* Otherwise, the monkey would not be rewarded and the trial would be labeled as *incorrect*, yet the trial would be included in the analysis, because the monkey's touch-bar response indicated that he perceived the second stimulus pair as occurring first. Similarly, on non-match trials, if the monkey released the touch-bar after the second pair of stimuli turned green, he would be rewarded and the trial would be labeled as *correct*. However, if the monkey treated the trial as a match and released the bar during the first

response period, this trial would be labeled as incorrect with no ensuing reward, yet the animal's response indicated that he perceived the first stimulus pair as appearing second.

If the animal released the bar before or up to 200 ms before the green cue, the trial was aborted without reward, because it would have been impossible (or unlikely) for the animal to process information about the type of hand response until that moment. These trials were extremely rare (average percentage per session: monkey E, 0.4%; monkey M, 0.2%). During non-match trials, if the monkey did not release the touch-bar within 750 ms after the second stimulus pair turned green, the trial would not be included in further analysis, because maintaining contact with the touch bar was considered uninformative regarding the animal's temporal order perception. These trials were also rare (average percentage per session: monkey E, 1.3%; monkey M, 2.1%).

3.2.3 Neuronal Recording and Identification of LIP units

For neuronal recording, the dura was penetrated using a 26 mm guide tube and grid system (Crist, Yamasaki, Komatsu, & Wurtz, 1988). Signals from the electrode were amplified (BAK Electronics), filtered (band pass from 0.4 to 6 kHz) and fed into a dual window discriminator (BAK Electronics) for isolation of action potentials, recorded at 1 ms resolution. Spike and eye-position recording, stimulus presentation and task control were handled by a computer running custom software.

During each recording session, a neuron would be isolated and verified as an LIP cell, based on sulcal anatomy (from structural MRI) and physiological properties. LIP

was identified using the memory-guided delayed saccade task (Barash, Bracewell, Fogassi, Gnadt, & Andersen, 1991). In this task the animal is required to remember the location of a flashed stimulus presented while it is fixating and make a delayed saccade to the remembered location of the stimulus, which is no longer present (Hikosaka & Wurtz, 1983a). During the period when the animal remembers the location of a saccade target, many LIP units show spatially specific sustained (delay) activity, often increasing before the initiation of the saccade (Barash et al., 1991; Colby, Duhamel, & Goldberg, 1996). Almost all of the cells in our study showed delay activity. The few remaining cells not exhibiting delayed activity were localized to the lateral bank of intraparietal sulcus (and thus designated as LIP units) because they were located within ~1 mm from units with delayed activity, with no obvious intervening white matter transition. After a unit was isolated and tested with the memory delayed saccade task, its receptive field (RF) was mapped using an automated routine in which a small spot was flashed (100 ms on, 200 ms off) in pseudo-random fashion over an imaginary grid of possible locations covering the region of interest in the visual field. Units were first tested with an 8 × 8 grid (vertical separation 3.8°; horizontal separation 2.7°), followed by a more localized grid with a higher spatial resolution (depending on the first map: 4-5 spots per side, vertical separation 1.0 -1.5°, horizontal separation 1.0 -1.5°). The latter was used to find the location in the RF that elicited the strongest response to the flashed spot (Ben Hamed, Duhamel, Bremmer, & Graf, 2001; Fanini & Assad, 2009). This location was taken as the center of the RF, and the three other circles in the stimulus were configured relative to it as described above. Recorded units were confined to those eliciting a visual response (excitatory or inhibitory) in the mapping task(s); visually unresponsive units were not

examined further. The monkey then performed the TOJ task while we simultaneously recorded the neural activity. Neuronal data was collected as long as isolation could be maintained and the animal continued to perform the task.

3.2.4 Display Apparatus

Stimuli were presented on a CRT monitor (832 × 624 pixel resolution, 120 Hz vertical refresh rate, 8.3 ms per frame) located 57 cm from the monkey's eye and subtending 38.6° horizontally and 29.5° vertically.

3.3 Results

3.3.1 Behavioral Data

For each neuron that we recorded, the stimulus configuration for the TOJ experiment was chosen to conform to the location of the neuron's receptive field. After we mapped the receptive field, the four white circles were configured such that one fell inside the receptive field. The other circle in the pair always appeared on the same video frame in the opposite visual hemifield. This pair of stimuli, with one of the circles of the pair falling in the receptive field of the isolated unit, will be referred to as the RF-stimulus, whereas the other pair would be called nonRF-stimulus (Notice that RF-stimulus and nonRF-stimulus are both composed of a pair of circles).

During each session, the animal was presented with a range of SOAs; When the RF-stimulus appeared after the nonRF-stimulus, the SOA was defined as *negative*; when the RF-stimulus preceded the nonRF-stimulus, the SOA was defined as *positive*. The SOAs used in the experiment were 0, ±9 ms, ± 17 ms, ±25 ms, ±42 ms and ± 92 ms for monkey M, and 0, ±9 ms, ± 17 ms, ±34 ms, ±67 ms and ± 126 ms for Monkey E. SOAs were chosen in a truly random fashion on each trial, as was the required bar-release response (match vs. non-match).

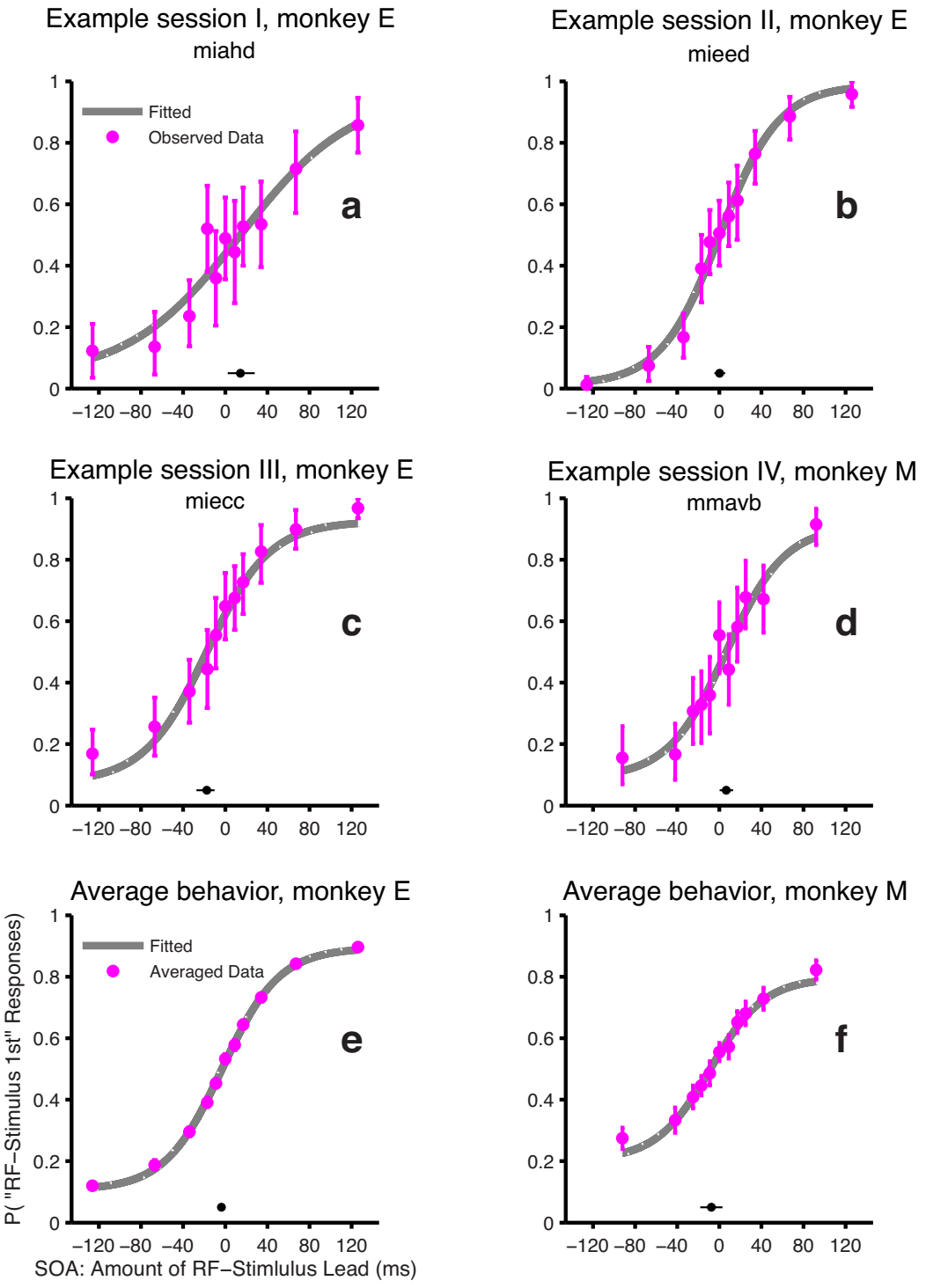
Figure 4a-d shows behavioral data for single sessions (4a-c, Monkey E; 4d, monkey M). To quantify the animal's performance, the percentage of trials in which the animal reported the nonRF-stimulus appearing after the RF-stimulus is plotted as a function of SOA. The data was fitted with a modified logistic function with three free parameters, as follows:

$$f(x) = \gamma/(1 + e^{\beta(x-\alpha)}) + (1-\gamma)/2$$

where x is the SOA, α is the bias, β is the slope of the curve, and γ is the maximum value of the function. Figure 4e-f shows averaged data for monkey E and monkey M, respectively. (Mean absolute bias (|α|): monkey E, 50 sessions, 14 ms; monkey M, 15 sessions, 31 ms; average max (γ) across sessions: monkey E, 50 sessions, 0.91; monkey M, 14 sessions, 0.89; median slope (β) across sessions: monkey E, 50 sessions, - 0.038; monkey M, 15 sessions, - 0.028; median of thresholds (threshold defined as SOA corresponding to 82% maximum performance for each session), monkey E, 50 sessions, 34 ms; monkey M, 12 sessions, 41 ms).

Figure 4. Probability of reporting 'RF-stimulus 1st as a function of SOA. SOA is defined as the "RF-stimulus lead", and is thus positive when the RF-stimulus is presented first (positive values on abscissa) and negative when RF-stimulus is presented second (negative values on abscissa). **(a-d)** correspond to different behavioral sessions (**a-c** from monkey E, **d** from monkey M). In each panel, magenta dots correspond to data obtained from the session, while the gray line is the fit with a modified logistic function. Magenta bars show 95% confidence intervals obtained through bootstrapping the data (1000 iterations). The black dot is the bias observed (parameter α in the fitted function), and the black line saddling it indicates the 95% confidence interval, obtained through bootstrapping the data (1000 iterations), and finding the bias value for each iteration. **(e-f)** Average of behavioral sessions (**e**, monkey E, 50; **f**, monkey M, 16). Magenta dots show the average values across sessions at each SOA while the error bars represent ± 1 standard error of mean (too small in monkey E, covered by value data). Gray line shows the fit to the averaged data. Black dot shows the bias of the fitted data, and the black line saddling it indicates the 95% confidence interval, obtained through bootstrapping the averaged data (1000 iterations). The SOAs used in the experiment: monkey E: 0, ±9 ms, ± 17 ms, ±34 ms, ±67 ms and ± 126 ms; monkey M: 0, ±9 ms, ± 17 ms, ±25 ms, ±42 ms and ± 92 ms. The five letter strings in **a-d** denote the file name of the unit for those individual sessions.

Figure 4 (Continued)



3.3.2 Neuronal Data

Extracellular recordings were made from 66 single units (50 from Monkey, right hemisphere; 16 from monkey M: 12 units right hemisphere, 4 units left hemisphere) using tungsten microelectrodes (FHC) (~1 MΩ at 1 kHz) in LIP. For monkey E, the range of total trials among neurons was 528-1302 (median 869); for monkey M the range was 372-1407 (median 747).

For the neurons recorded, the range of RF eccentricities was 4.7-18.9° in monkey E and 7.5-18° in monkey M. For some neurons, the RF was so eccentric that all four stimuli could not fit on the monitor. These neurons were not tested with the TOJ task.

3.3.2.1 Surround Modulation

When responses of each cell were aligned to the appearance of RF-stimulus, the onset of the stimulus in RF triggered a transient response, sometimes followed by a sustained response, as previously described in LIP (Bisley et al., 2004; Goldberg, Bisley, Powell, & Gottlieb, 2006). Yet this response was occasionally modulated by the nonRF-stimulus, much like a "surround" effect. As described in Methods, in the TOJ task the two circles comprising the nonRF-stimulus fell outside the region eliciting the strongest response (i.e., the RF). Note that one of the circles comprising the nonRF-stimulus would always fall in the hemifield opposite the RF, and the other one in same hemifield as the RF, but both non-RF circles would be distant from the RF.

Figure 5. Four LIP units showing different types of "surround modulation". Each panel (a-d) shows a peristimulus time histogram for the unit, shown separately for each SOA and aligned to the appearance of RF-stimulus (vertical gray line). The red arrow indicates the onset time of the nonRF-stimulus. **(a)** Unit with no detectable surround modulation. **(b)** Unit that shows surround modulation with little visual response to the nonRF-stimulus ("silent suppression"). **(c)** Unit that shows surround modulation along with a weaker visually evoked response to the "nonRF"-stimulus. **(d)** Unit that is suppressed following presentation of the RF-stimulus, but also suppressed following nonRF-stimulus. Number above each subpanel indicates the SOA, with negative values denoting that the nonRF-stimulus appeared first. Single-trial responses were averaged and then convolved with a Gaussian (SD of 10 ms). Unit (a) comes from monkey M, and units (b-d) come from monkey E. The behavioral session corresponding to unit (c) is shown in Figure 4a. Five letter strings correspond to the name of the unit.

Figure 5 (Continued)

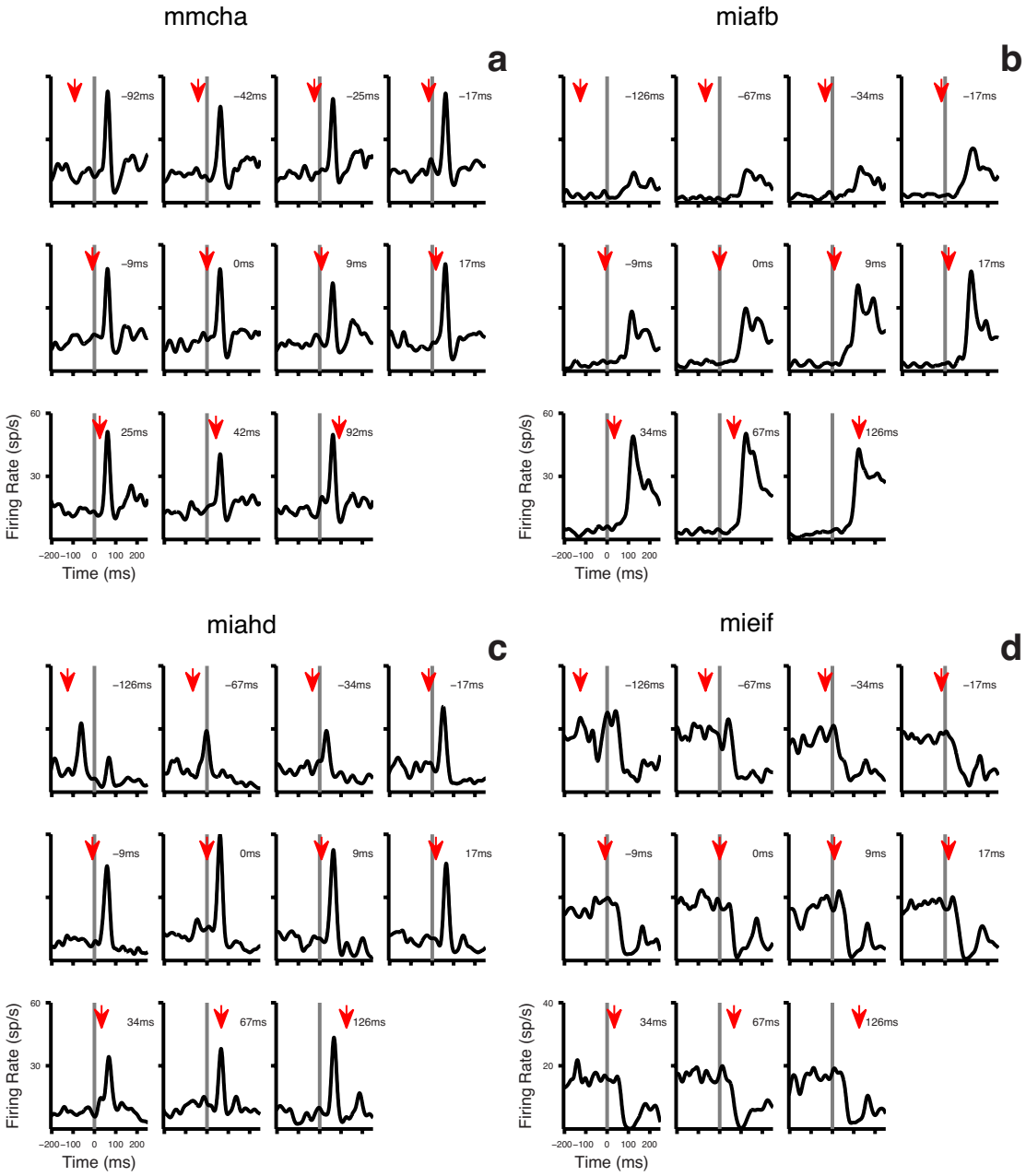


Figure 5 shows the responses of four LIP neurons as a function of SOA. In all cases, the responses are aligned on the onset of the RF-stimulus (black vertical line), and the time of the onset of the nonRF-stimulus is indicated by the red arrows. Figure 5a shows the most common type of effect (Monkey E: 38% ; monkey M: 75%) -- little modulation of the RF responses as a function of when the nonRF-stimulus appeared. Figure 5b shows a less common pattern of response, in which the nonRF-stimulus strongly suppressed the visual response when it preceded the RF-stimulus (for example, compare the visual evoked response in the -126 ms and -67 ms conditions with the +126 ms and +67 ms conditions). However, the nonRF-stimulus itself did not evoke a detectable response in the neuron, suggesting a sort of "silent suppression". Figure 5c shows modulation similar to that of 5b; however, there was a noticeable visual response elicited by the nonRF-stimulus (clear when the nonRF-stimulus appeared the earliest, -126 ms and -67 ms SOA conditions). In these cases, the nonRF-stimulus evoked a direct response, suggesting (by definition) that it encroached on the RF. Finally, we rarely observed more complex patterns of modulation. For example, the neuron in Figure 5d was suppressed by the RF-stimulus, but also appeared to be suppressed directly by the nonRF-stimulus (e.g., -126 ms SOA). Interestingly, the direct suppression caused by the nonRF-stimulus appeared to reduce the suppressive response of the RF-stimulus (compare -126 ms & -67 ms SOAs vs. +126 ms and +67 ms SOAs).

To quantify the effect, we performed a one-way ANOVA with 11 levels (eleven SOAs) on the spike counts. The ANOVA was performed on three different periods with respect to appearance of RF-stimulus: -50 to 40 ms, 40 to 100 ms and 100 to 250 ms. The number of units showing an effect of SOA (surround effects) ($P < 0.1$) is as follows:

monkey E: -50 to 40 ms, 20 (out of 50); 40 to 100 ms, 31 (out of 50); 100 to 250 ms: 43 (out of 50); monkey M: -50 to 40 ms, 5 (out of 16); 40 to 100 ms, 4 (out of 16); 100 to 250 ms, 7 (out of 16). A non-parametric test (Kruskal-Wallis) showed similar results: monkey E: -50 to 40 ms, 25 (out of 50); 40 to 100 ms, 28 (out of 50); 100 to 250 ms: 44 (out of 50); monkey M: -50 to 40 ms, 5 (out of 16); 40 to 100 ms, 4 (out of 16); 100 to 250 ms, 7 (out of 16).

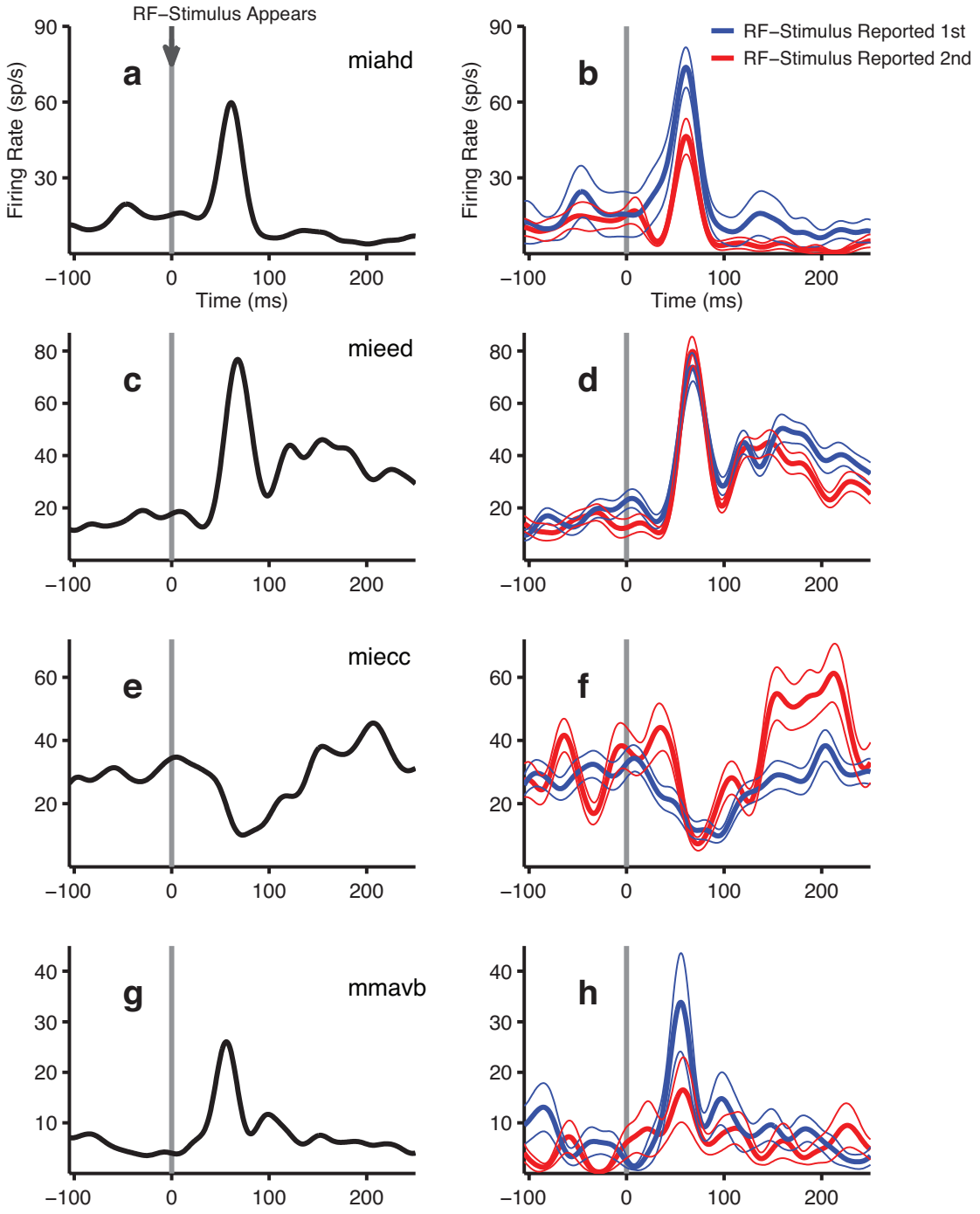
While surround effects have well been established in other cortical areas (see Discussion) surround effects of this sort have not been previously described in LIP. Goldberg and colleagues have reported suppressive effects in LIP, but the modulation they observed was in the context of making saccades rather than stimulus-evoked visual responses (Falkner, Krishna, & Goldberg, 2010). While visual surround effects will be interesting to examine in more detail in future studies, for our purposes here they suggest that we must be careful when comparing neuronal responses between different SOAs.

3.3.2.2 Single units are modulated in TOJ task

Our goal was to examine differences in neuronal responses when the monkey reports that one or the other visual stimulus appeared first; these differences could be related to the animal's perception of temporal order. Figure 6 shows the response profiles of four LIP units in the TOJ task. Figure 6a-b shows an LIP unit with phasic visual response, Figure 6c-d displays a unit with phasic and tonic response, and Figure 6e-f depicts a unit that is suppressed by visual stimulation; all three units were from monkey E. Figure 6 g-h is an example from monkey M. Because we observed an effect of SOA

Figure 6. Responses of single LIP units in the TOJ task (SOA= 0 ms). Left panels (**a, c, e, g**) show spike-rate functions for four different units aligned to the onset of the RF- and nonRF-stimuli (presented simultaneously for SOA=0). Right panels (**b, d, f, h**) depict data from the same (left-side) unit but with neural activity shown separately depending on whether the animal reported the RF-stimulus appearing first (blue) or second (red), where the same color thin lines show ± 1 standard error of mean. **(a)** Unit with phasic response. **(c)** Unit with both phasic and tonic response. **(e)** Suppressed unit. Units (**a, c, e**) are from monkey E. **(g)** Another unit with phasic response, from monkey M. The gray vertical line represents the time of onset of the RF-stimulus (and nonRF-stimulus). Spike-rate functions for individual units were generated by convolving 1-ms-binned histograms with a Gaussian (SD of 10 ms). Five letter strings indicate the file name for each unit. Units are the same as those in Figure 4 a-d.

Figure 6 (Continued)



on the amplitude of the visual responses (discussed above), the visual response and the effect of perceptual report must be studied *within* each SOA condition to ensure that any difference in neuronal response is not due to differences in the visual stimulation. The left column in Figure 6 shows the average response of all trials with SOA=0 ms, aligned to the onset of the RF-stimulus (for SOA=0 ms condition, the nonRF-stimulus also appears at this same time). The right column shows the responses divided according to whether the animal reported the RF-stimulus appearing first or second. Note that the responses (RF-stimulus reported first vs. second) are pooled across both the match and non-match conditions since the monkey has no information regarding the required touch-bar response until the green spots appear.

When the neural responses were divided according to the animal's perceptual report (Figure 6, right column), there was a difference in firing pattern as a function of perceptual report. When the animal judged that the RF-stimulus appeared first (blue trace), the firing rate was higher during the transient visual response, and then remained slightly higher, on average, following the transient response (Figure 6b: peak activity ± 1 SEM, RF-stimulus reported 1st: 73.7 ± 8 Hz, RF-stimulus reported 2nd: 46.4 ±7 Hz; mean activity 100-250 ms after RF-stimulus, RF-stimulus reported 1st: 10 ± 5.6 Hz, RF-stimulus reported 2nd: 2.7 ± 1.7 Hz). For the unit that was suppressed by the visual stimulus (Figure 6e-f), the unit showed more suppression when the animal reported the RF-stimulus first (Figure 6f: trough activity ± 1 SEM, RF-stimulus reported 1st: 6.7 ± 1.7 Hz, RF-stimulus reported 2nd: 7.2 ± 2.1 Hz; mean activity 100-250 ms after RF-stimulus, RF-stimulus reported 1st: 27.9 ± 3.9 Hz, RF-stimulus reported 2nd: 43.4 ± 7 Hz); in other words, the perceptual modulation seemed to follow the visual modulation of the unit.

This perceptual effect was not limited to the SOA=0 ms condition. Figures 7 & 8 show the same four units' visual response and perceptual modulation when the SOA was -9 ms and +9 ms, respectively. For these conditions in which the SOA was nonzero, the data include both correct and incorrect trials, as well as match vs. non-match trials.

Figure 7. Responses of single LIP units (SOA= -9 ms). Left panels (**a, c, e, g**) show spike-rate functions for four different units aligned to the RF-stimulus, with the nonRF-stimulus presented one frame (9 ms) before. Individual units are the same as those shown in Figure 6. Figure conventions are the same as in Figure 6.

Figure 7 (Continued)

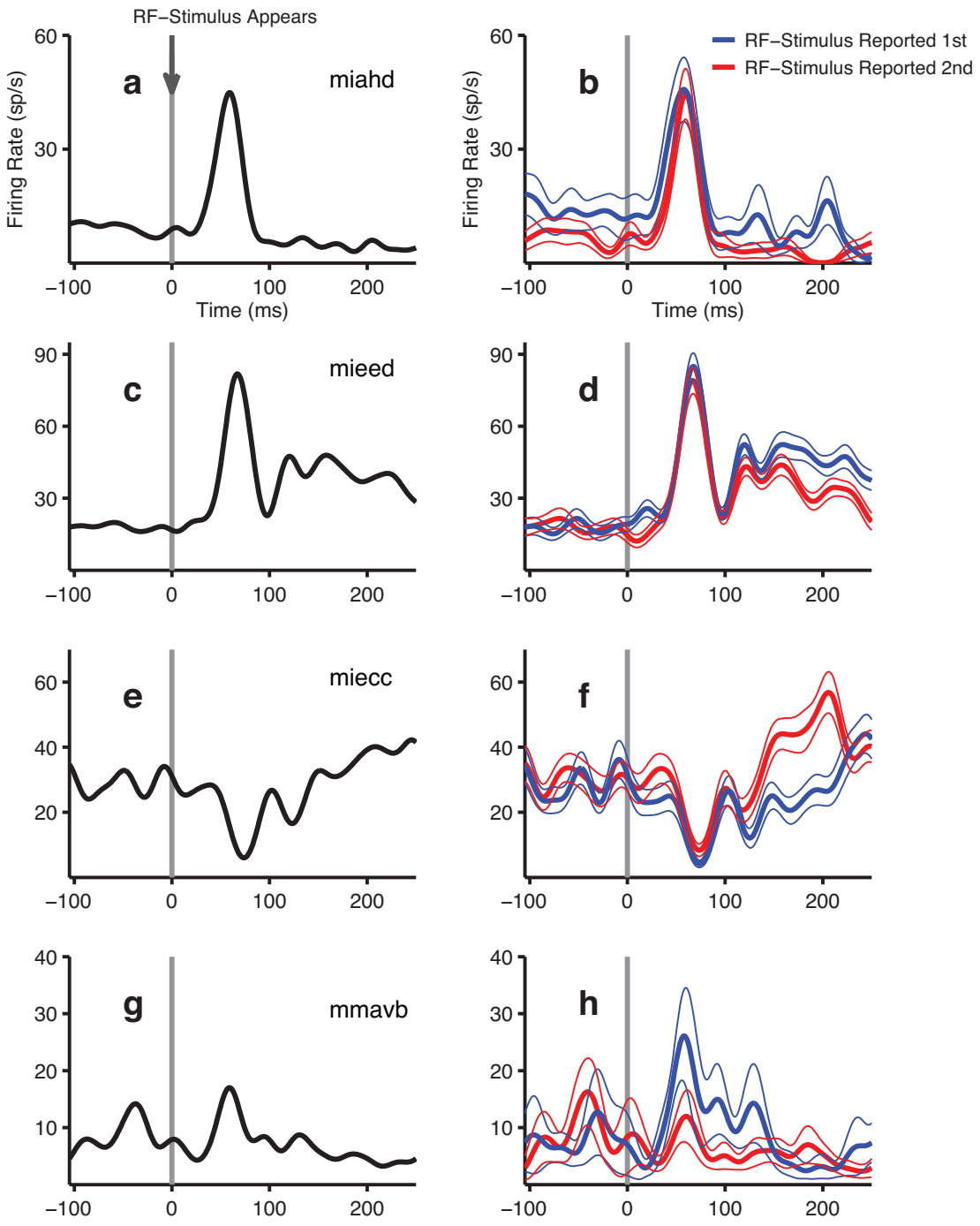
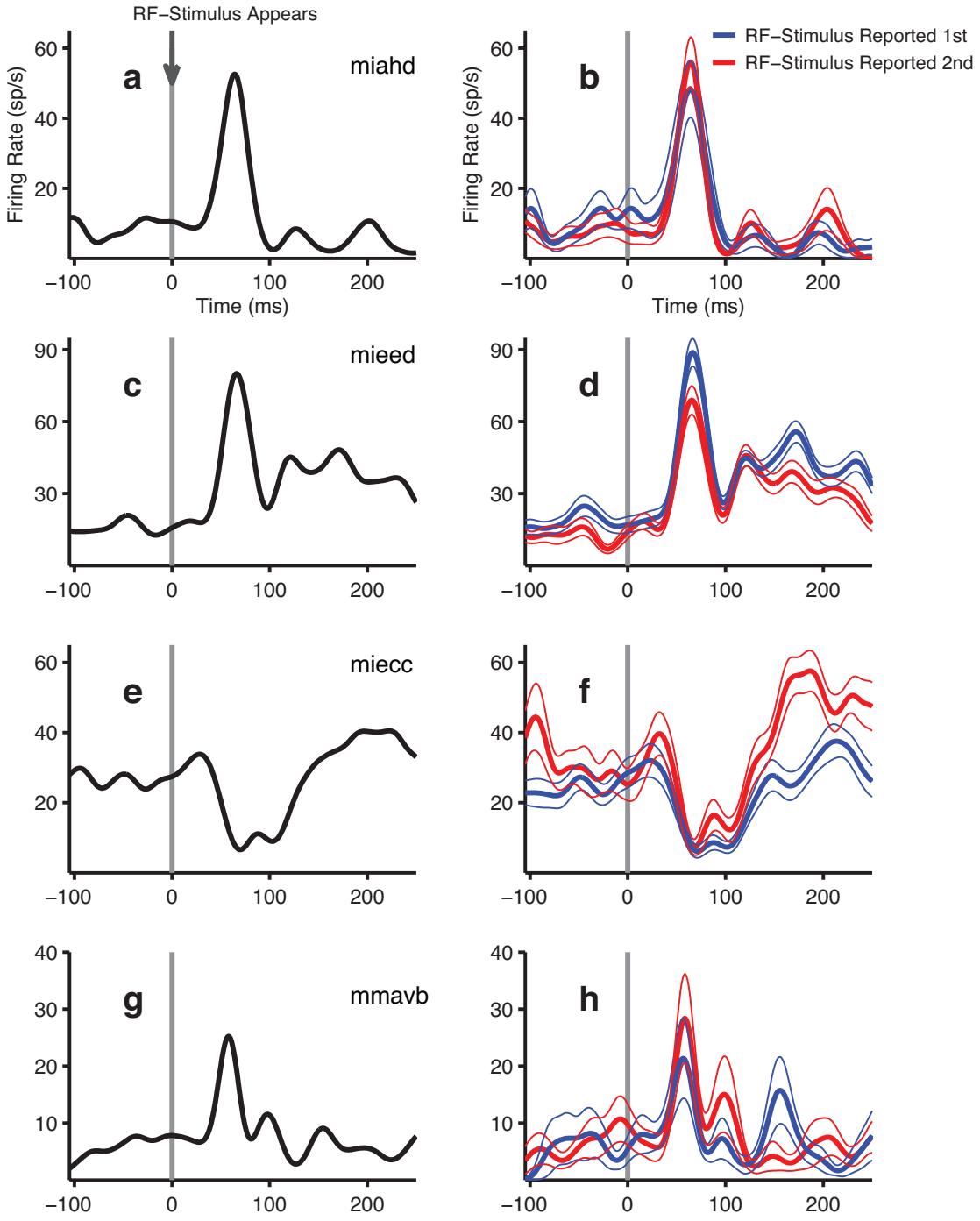


Figure 8. Responses of single LIP units (SOA= +9 ms). Left panels (**a, c, e, g**) show spike-rate functions for four different units aligned to the RF-stimulus, with the nonRF-stimulus presented one frame (9 ms) later. Individual units are the same as those shown in Figure 6. Figure conventions are the same as in Figure 6.

Figure 8 (Continued)



3.3.2.3 Population Data

The average population response for each animal (monkey E, 50 units; monkey M, 16 units) showed a similar pattern of modulation. (Figure 9a-l, SOAs 0 ms, -9 ms and +9 ms; each animal showed separately).

To quantify the effect of perceptual report, for each unit we calculated choice probability (CP), a method derived from signal-detection theory (Britten, Newsome, Shadlen, Celebrini, & Movshon, 1996; Dodd, Krug, Cumming, & Parker, 2001; Liu & Newsome, 2005; Nienborg & Cumming, 2006; Uka, Tanabe, Watanabe, & Fujita, 2005). For each cell, we are provided with two distributions of spike counts, each corresponding to one perceptual choice. We calculated CP within an individual SOA condition to ensure that the visual stimulus was identical and only the perceptual choice was different. CP tells us how distinct these two distributions are: the more separate these two distributions, the larger the area under the receiver operating characteristic (ROC) curve (expressed as CP), making it more likely to correctly predict the animal's behavior based on the firing rate on a single trial. Thus CP indicates how much the trial-by-trial variability in neuronal responses is correlated with the animal's behavioral choice. CP values vary between 0 and 1.0, depending on the separation between the two distributions of spike counts for each perceptual choice. In our study, 1.0 indicates that the cell fired more on all trials in which the animal judged that the RF-stimulus appeared first, whereas 0 would mean the cell fired more whenever the animal reported the opposite temporal order. A CP of 0.5 indicates that the cell fired equally strongly for the two choices and thus did not convey any information regarding the animal's temporal order judgment. On the other hand,

neurons with CPs significantly different than 0.5 indicate that the cell's firing is related to the animal's perceptual report.

The time period during which we focused our CP analyses was 50 ms before the stimulus appeared in the RF until 250 ms after the stimulus appeared in the RF. Note that throughout this time interval, the animal did not yet have any information regarding the appropriate hand response (match vs. non-match).

We divided this time period into three separate time windows, with respect to the appearance of the RF-stimulus:

i) Baseline period: from -50 to 40 ms

ii) Phasic period: 40 to 100 ms after onset of RF-stimulus: this period captures the transient response of the neuron

iii) Tonic period: 100 to 250 ms after RF-stimulus appearance: this period represents the sustained response of the neuron

Although we found response latencies around 50 ms in our LIP units (see below), we restricted our baseline period to 40 ms after stimulus onset to avoid contamination from the visual onset response.

Figure 9. Population data, LIP. Left panels (**a, c, e, g, i, k**) show population-average spike rates for three different SOAs, aligned to the appearance of RF-stimulus. Right panels **(b, d, f, h, j, l**) correspond to the same condition shown to the left, but with neural activity shown separately depending on whether the animal reported that the RF-stimulus appeared first (blue) or second (red). Panels on the odd rows show data from monkey E; panels on even rows show data from monkey M. **(a-d)** SOA= 0 ms, **(e-h)** SOA=-9 ms, **(i-l)** SOA=+9 ms. The gray vertical line represents the time at which RF-stimulus appeared. Spike rates (1-ms binned) for individual units were averaged and then convolved with a Gaussian (SD of 4 ms).

Figure 9 (Continued)

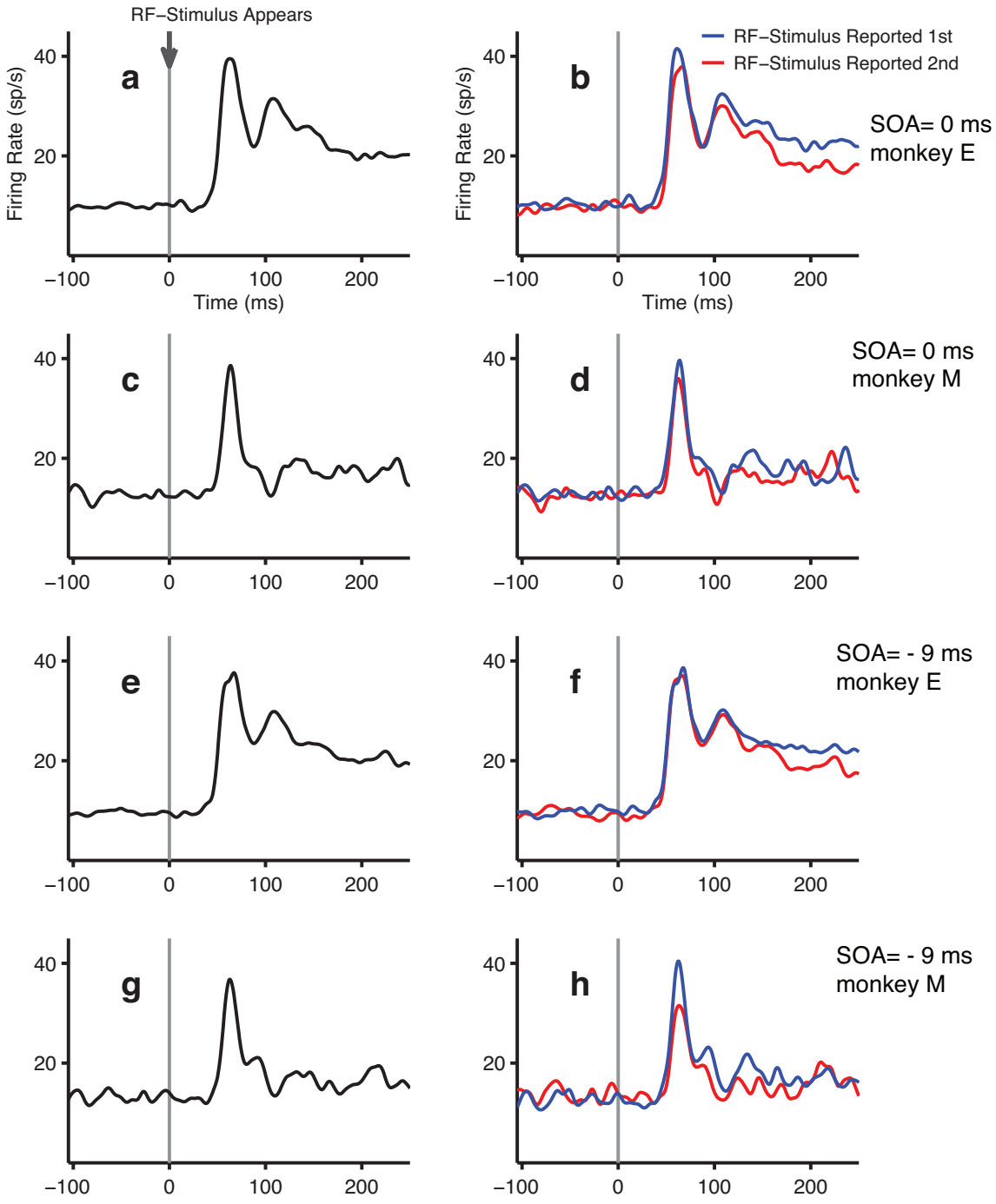
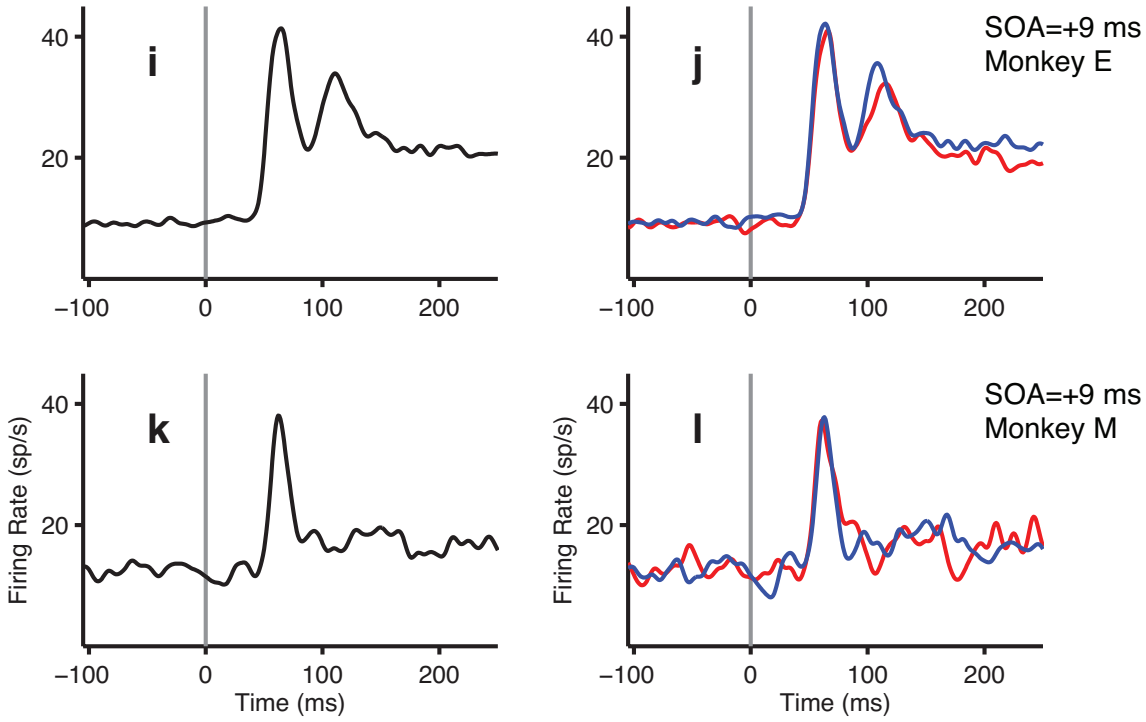


Figure 9 (Continued)



For each of the periods, we calculated CPs for the SOA=0 ms (Figure 10), as well as SOA=±9 ms (Figure 11). The SOA=0 ms condition is the most favorable (to analyze) because the number of choices (RF-stimulus first vs. RF-stimulus second) was close to equal. However, similar results were obtained for the SOA=±9 ms conditions. Table 1 contains the mean CP, *p*-value (significance of CP distribution different from 0.5, t-test, two-tailed) and number of units with significant CP values (obtained through permutation test, 2000 iterations) for each time period and for each animal separately in the SOA=0 ms condition. Table 2 contains those values for SOA= -9 ms and SOA=+9 ms.

Similar patterns for CP distributions can be seen across different SOAs: in monkey E, the CP distributions were not significantly different from 0.5 in the baseline period, while they became larger (phasic and tonic period) and statistically significant (tonic period) at later time intervals. Though monkey M's data was significant in only one condition (SOA=-9 ms, 40 to 100 ms after RF-stimulus onset), the same trend can be observed: CP distributions not significantly different from 0.5 during the baseline period, while CPs > 0.5 at later time intervals.

Figure 10. Histogram of choice probability (CP) distribution, LIP units, SOA=0 ms condition. Top row (**a-c**) shows data from monkey E, bottom row (**d-f**) from monkey M. Each column corresponds to a different time period over which CP was calculated: **a, d**: -50 to 40 ms, **b, e**: 40 to100 ms, **c, f**: 100 to 250 ms. Arrow shows the mean CP across the population for that histogram. Red vertical line is drawn at CP=0.5. Neurons with statistically significant CPs are shown as black bars. Significance for each unit was calculated through a permutation test (2000 iterations). Stars next to mean CP value indicate significance of CP distribution different from 0.5. * p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001, two-tailed t-test.

Figure 10 (Continued)

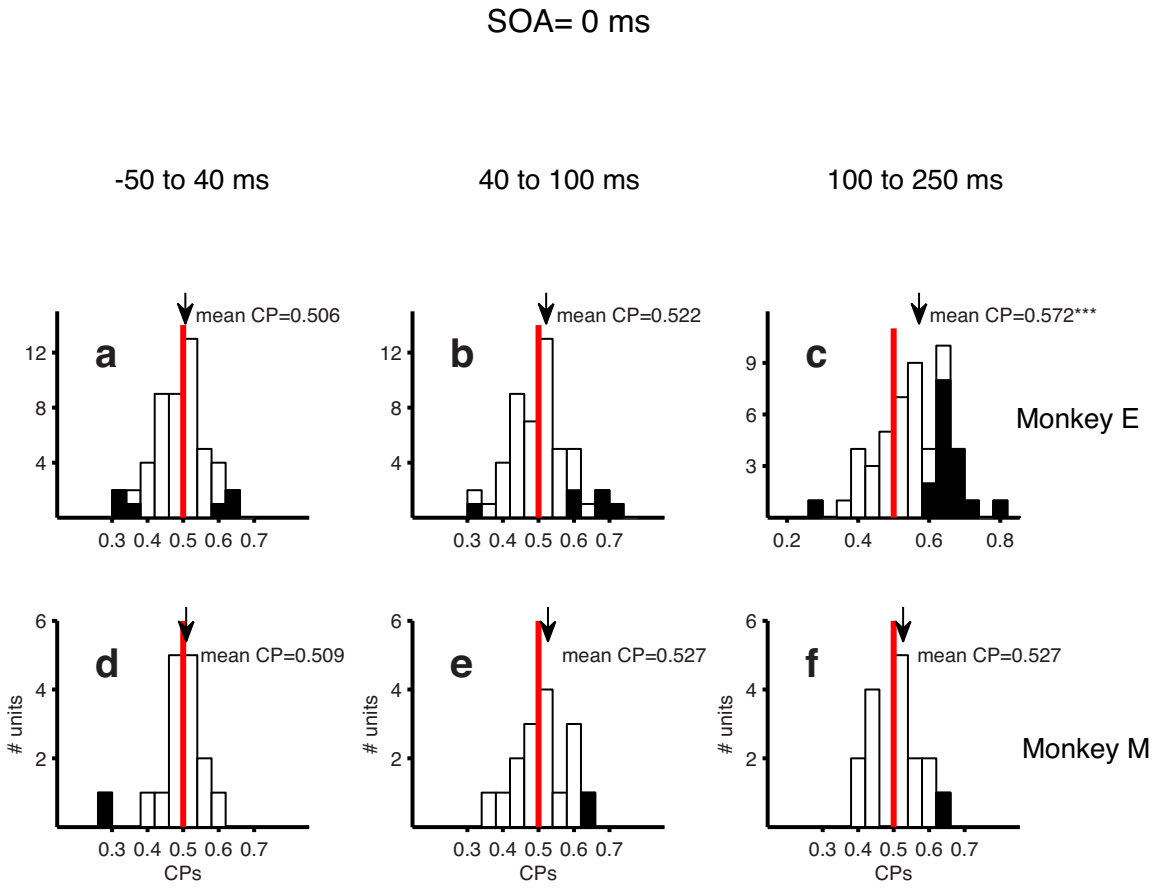


Figure 11. Histogram of choice probability (CP) distribution, LIP units, SOA= ± 9ms condition. Top two rows **(a-f)** show data for SOA= -9 ms, bottom two rows (**g-l**) depict data for SOA= +9 ms. First and third rows **(a-c, g-i)**, monkey E; second and fourth rows **(d-f, j-l)**: monkey M. Each column corresponds to a different time period over which CP was calculated: **a, d, g, j**: -50 to 40 ms, **b, e, h, k**: 40 to100 ms, **c, f, i, l**: 100 to 250 ms. Arrow shows the mean CP across the population for that histogram. Red vertical line is drawn at CP=0.5. Neurons with statistically significant CPs are shown as black bars. Significance for each unit was calculated through a permutation test (2000 iterations). Stars next to mean CP value indicate significance of CP distribution different from 0.5. * p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001, two-tailed t-test.

Figure 11 (Continued)

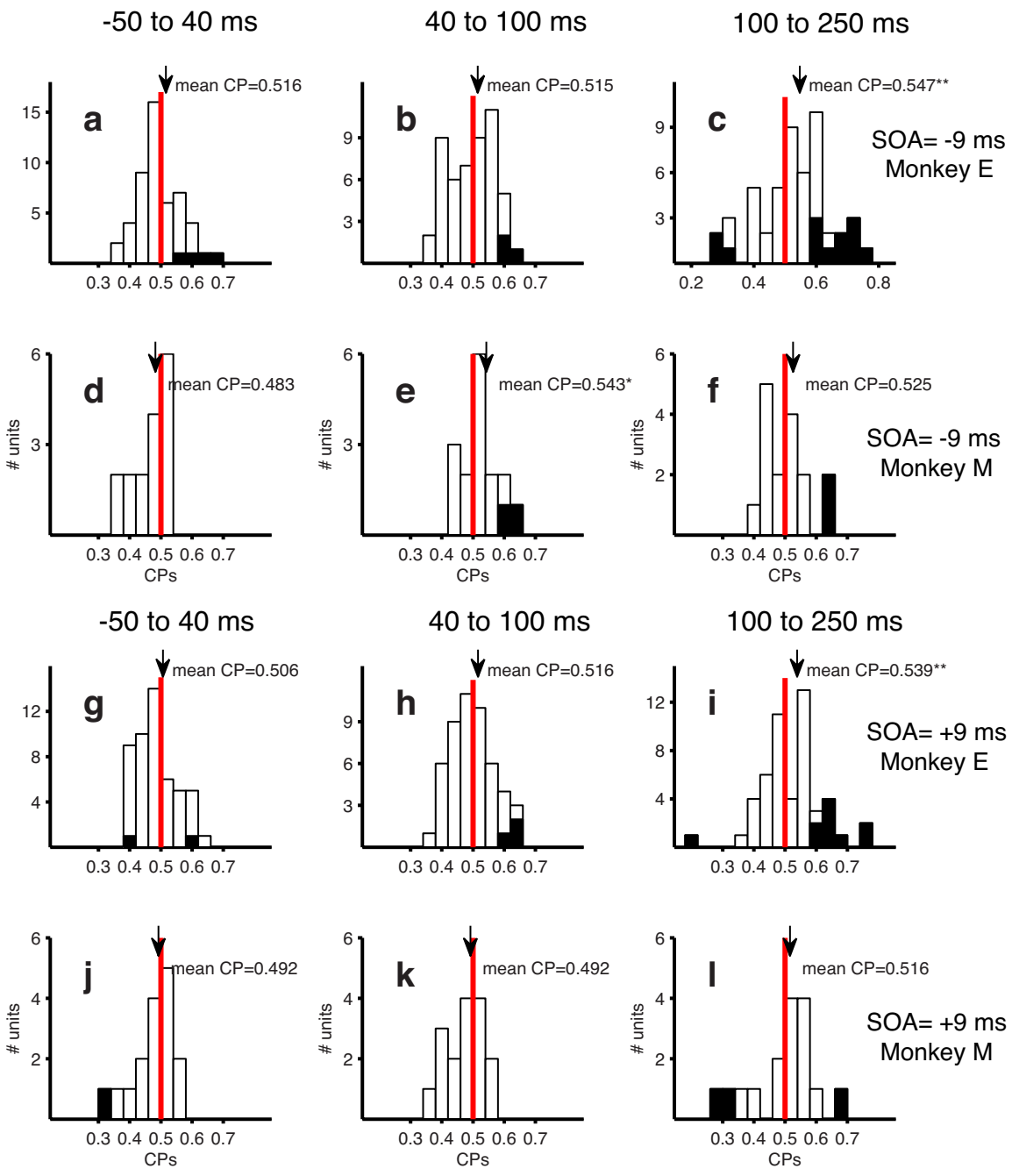


Table 1

Table 1	SOA= 0 ms: mean CP, *p*-value, # of significant units, # total units		
	-50 to 40 ms	40 to 100 ms	100 to 250 ms
Monkey E	0.506 (0.55) 6 (50)	0.522 (0.09) 6(50)	0.572 (8.63e-06) 17(50)
Monkey M	0.509 (0.65) 1 (16)	0.527 (0.16) 1 (16)	0.527 (0.16) 7 (16)

Table 1. SOA= 0 ms. Mean CP, *p*-value (significance of CP distribution different from 0.5, t-test, two-tailed), number of significant units (permutation test, 2000 iterations) alongside the total number of units recorded, shown for each time period -50 to 40 ms, 40 to 100 ms and 100 to 250 ms. Data is shown for each animal separately. Mean CP and *p*-value are on the first row in each table cell. The number of units with statistically significant CP and total number of units are on the second row.

Table 2

Table 2	SOA= -9 ms: mean CP, *p*-value, # of significant units, # total units		
	-50 to 40 ms	40 to 100 ms	100 to 250 ms
Monkey E	0.516 (0.11) 4 (50)	0.515 (0.14) 3 (50)	0.547 (0.006) 13 (50)
Monkey M	0.483 (0.3) 0(16)	0.543 (0.01) 2 (16)	0.525 (0.18) 2(16)
	SOA= +9 ms: mean CP, *p*-value, # of significant units, # total units		
	-50 to 40 ms	40 to 100 ms	100 to 250 ms
Monkey E	0.506 (0.5) 2 (50)	0.516 (0.11) 3 (50)	0.539 (0.007) 10 (50)
Monkey M	0.492 (0.65) 2 (16)	0.492 (0.55) 0 (16)	0.516 (0.56) 3 (16)

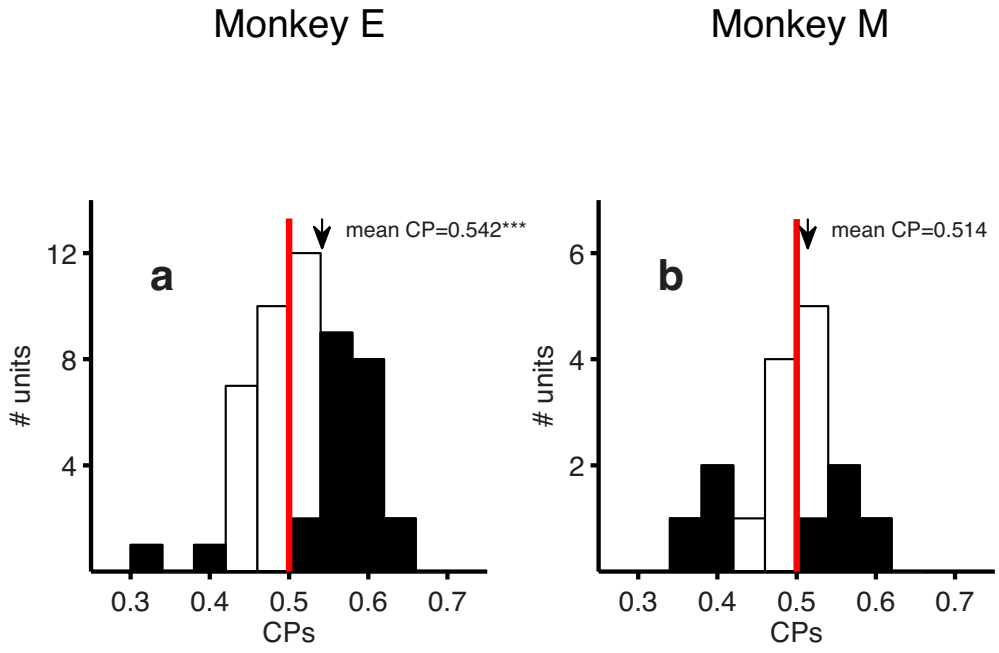
Table 2. SOA= ± 9 ms. Mean CP, *p*-value (significance of CP distribution different from 0.5, t-test, two-tailed), number of significant units (permutation test, 2000 iterations) alongside the total number of units recorded, shown for each time period -50 to 40 ms, 40 to 100 ms and 100 to 250 ms. Data is shown for each animal separately. Mean CP and *p*-value are on the first row in each table cell. The number of units with statistically significant CP and total number of units are on the second row.

Because the number of trials was small for each SOA, we also pooled data from different SOAs to increase our statistical power. Since the mean and variance of spike counts can vary among conditions, spike counts are usually z-scored before pooling and calculating CP – the so-called grand CP (Britten et al., 1996; Nienborg & Cumming, 2006). However, this method tends to underestimate the CP value when the ratio of trials per behavioral choice is different across conditions, as in our experiment. The reason is that simply z-scoring within each condition would lead to two distributions, each corresponding to one behavioral choice, with the height of one distribution multiple times greater than the other. For example, when the SOA is +126 ms, at one end of the psychometric function, the monkeys reported more than 90% of these trials as "RF-stimulus appeared first". Thus the height of the z-scored distribution for the "RF-stimulus first" would be more than 9 times that of the "RF-stimulus second", and thus its center much closer to 0 (on the z-score scale) compared to the other distribution. The opposite trend would happen for the SOA=-126 ms, for which the monkey reported almost all trials as "RF-stimulus second". Pooling across these two conditions would lead the composite CP to become closer to 0.5, since each choice contributes a large distribution slightly shifted from zero in opposite directions, cancelling each other out. To overcome this problem, we followed the procedure proposed by Kang & Maunsell (Kang & Maunsell, 2012): spike counts were z-scored, calculating the value within each SOA condition as if they had come from samples with an equal number of trials for each behavioral choice (balanced z-scoring). The balanced z-scores were then pooled across conditions, and the grand CP calculated.

To calculate the grand CP, we focused on the time period from 40-250 ms after onset of the RF-stimulus. Calculating the grand CP for the baseline period (-50 to 40 ms after RF-stimulus onset) would be problematic, since there were few spikes (< 3-4 per trial) in this time window for most of the cells. Pooling across conditions with different ratios of trials where the spike count is low also leads to artificially low CPs (Kang & Maunsell, 2012). To avoid this problem, the grand CP was calculated only over 40-250 ms after RF-stimulus appearance, encompassing both the phasic and tonic period of the response. Figure 12 shows the distributions of grand CPs calculated for each monkey separately. Mean CP (0.542) was highly significant for monkey E ($p < 0.001$). 23 out of 50 (46%) of units from monkey E and 7 out of 16 (44%) from monkey M showed significant grand CPs (permutation test, 2000 iterations).

Figure 12. Histogram of choice probability (CP) distribution, LIP units, calculated across all conditions (grand CP). (**a)** Monkey E, (**b**) Monkey M. CP was calculated from spike counts during the time period 40-250 ms after RF-stimulus onset. Arrow shows the mean CP across the population for that histogram. Red vertical line is drawn at CP=0.5. Neurons with statistically significant CPs are shown as black bars. Significance for each unit was calculated through a permutation test (2000 iterations). Stars next to mean CP value indicate significance of CP distribution different from 0.5. * p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001, two-tailed t-test.

Figure 12 (Continued)



3.3.2.4 Latency Analyses

It is plausible (and tempting to think) that the perception of a stimulus appearing earlier in time would be correlated with earlier neural activity in the cells encoding that visual stimulus. To test this hypothesis, we performed a visual latency analysis using a least-squares estimate (LSE) (DiCarlo & Maunsell, 2005). This approach assigns a squared error function to the data and finds the point in time at which the largest change in firing rate occurs. This is equivalent to finding the border at which the sum-of-squares differences on either side of the border is minimum. The minimum border is found by moving in steps of 1 ms over the time period -100 ms to 200 ms (unless specified otherwise) after RF-stimulus onset. At each step, on the left side of the border, the mean of neural activity is calculated, and afterwards spike rates (1-ms resolution) are subtracted from that mean, and the sum of the squared differences is calculated. The same procedure is performed for the right side of the border and the sum of squares differences from both sides are added. The border is moved across the whole time period, and the time point that yields the minimum of left-and-right sum of the squared differences is taken as the cell's visual response latency in that condition.

The advantage of the LSE method over statistical methods, such as deviation-from-Poisson (Maunsell & Gibson, 1992) is that it is not susceptible to a few noisy trials. In addition, because its not based on statistical criteria, it is less sensitive to the number of trials. For statistical measures of latency, different criteria can apply across different cells based on the number of trials.

Latency was measured as a function of perceptual report for each unit for SOA=0 ms, -9 ms and +9 ms. Latency was taken as the minimum of left-and-right sum of the squared differences from 30-110 ms after RF-stimulus onset. For some units the unsmoothed spike rate functions were too noisy due to small number of trials in each condition. For this reason, units that had an absolute latency difference of 15 ms or larger between the two perceptual choices were excluded, as well as units for which the latency was assigned to the descending part of the spike-rate function for either behavioral choice. The mean difference in latency as a function of the animal's order judgment was small (Figure 13), and approached significance (opposite to our hypothesis, latency report 1^{st} > latency report 2^{nd}) only in one condition (SOA= +9 ms) in monkey M. When the one unit with largest latency difference (latency reported 1^{st}, 44 ms; latency reported 2^{nd}, 31 ms) was removed, the mean latency difference (reported 1^{st} – reported 2^{nd} = 3.8 ms) was not significant (p= 0.11). Thus the small effect was unreliable. Table 3 shows the mean latency difference (RF-stimulus reported 1^{st} – RF-stimulus reported 2^{nd}), p-value and number of units satisfying the inclusion criteria.

To increase the power in our latency analysis, all trials were pooled across all units in each animal (separately for each SOA) and latency was calculated (Figure 14). Table 4 contains latency values and 95% confidence intervals, (bootstrap procedure, 2000 iterations) for the three SOAs. Latency differences and 95% confidence interval for latency differences (permutation test, 2000 iterations) are summarized in Table 5. None of the latency differences were statistically significant.

Figure 13. The effect of perceptual report on neural latencies in LIP units, calculated for each unit. Left column (**a, c, e)**, monkey E; right column (**b, d, f**), monkey M. Each row corresponds to one stimulus condition (SOA): top **(a-b)**, SOA= 0 ms; middle **(c-d)**, SOA= -9 ms; bottom **(e-f),** SOA= +9 ms. Each point corresponds to one unit. Neural latencies for RF-stimulus reported 2nd (abscissa) is plotted against those for RF-stimulus reported 1st (ordinate). Mean latency difference is reported for each condition. Red line corresponds to unity (y=x). Corresponding mean latency values and significance values for latency differences can be found in Table 3.

Figure 13 (Continued)

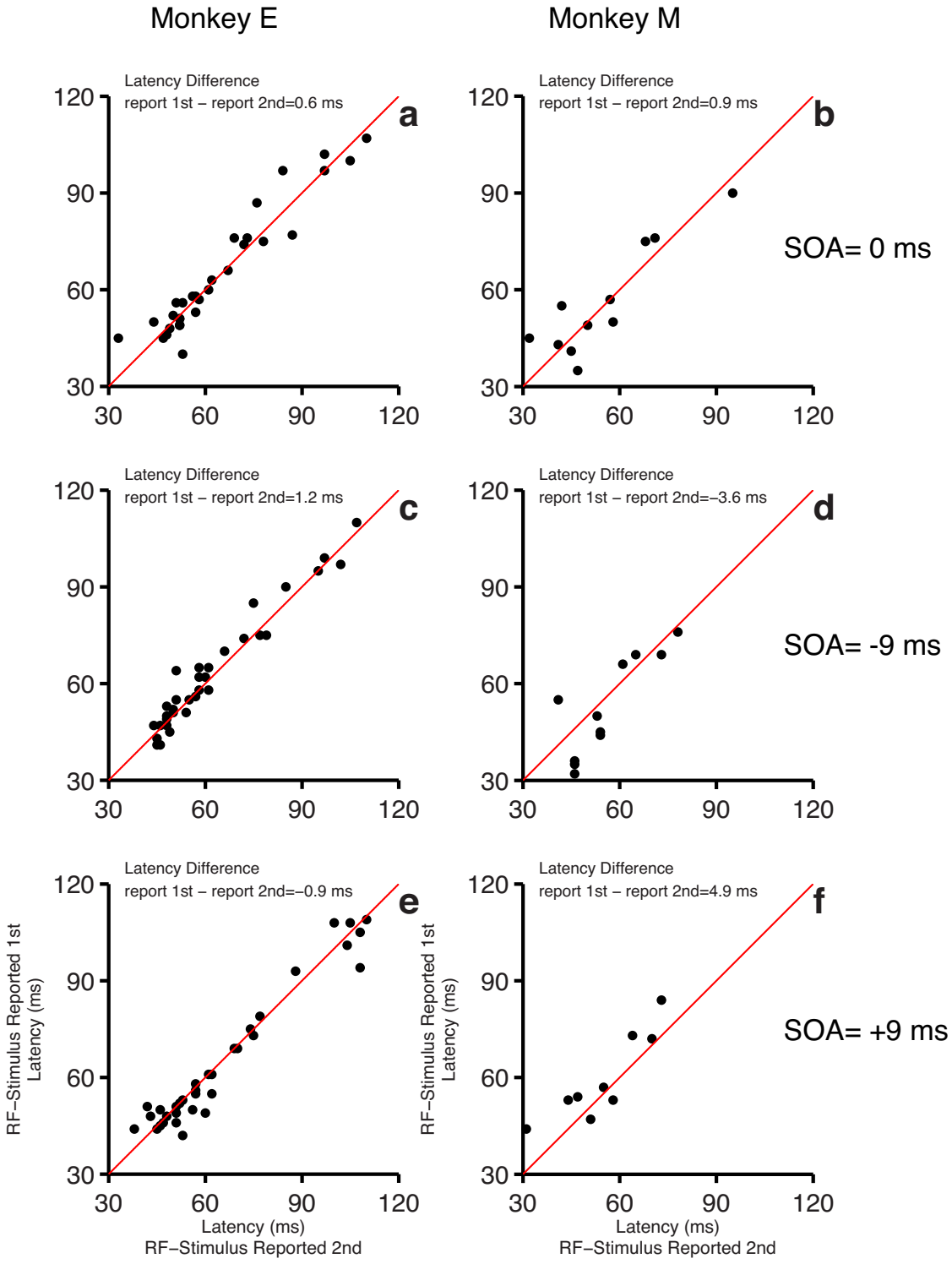


Figure 14. The effect of perceptual report on neural latencies in LIP units, calculated for pooled units. Left column (**a, c, e)**, monkey E; right column (**b, d, f**), monkey M. Each row corresponds to one stimulus condition (SOA): top **(a-b)**, SOA= 0 ms; middle **(c-d)**, SOA= -9 ms; bottom **(e-f)**, SOA= +9 ms. Spike-rate functions were generated by averaging all single trials (1-ms-binned histograms) across all units (unsmoothed). Neural activity is aligned to the appearance of RF-stimulus (vertical gray line), shown separately depending on whether the animal reported the RF-stimulus appearing first (blue) or second (red), where the same arrow colors indicate calculated latency for the corresponding choice. Corresponding latency values and 95% confidence intervals for latency differences can be found in Tables 4-5.

Figure 14 (Continued)

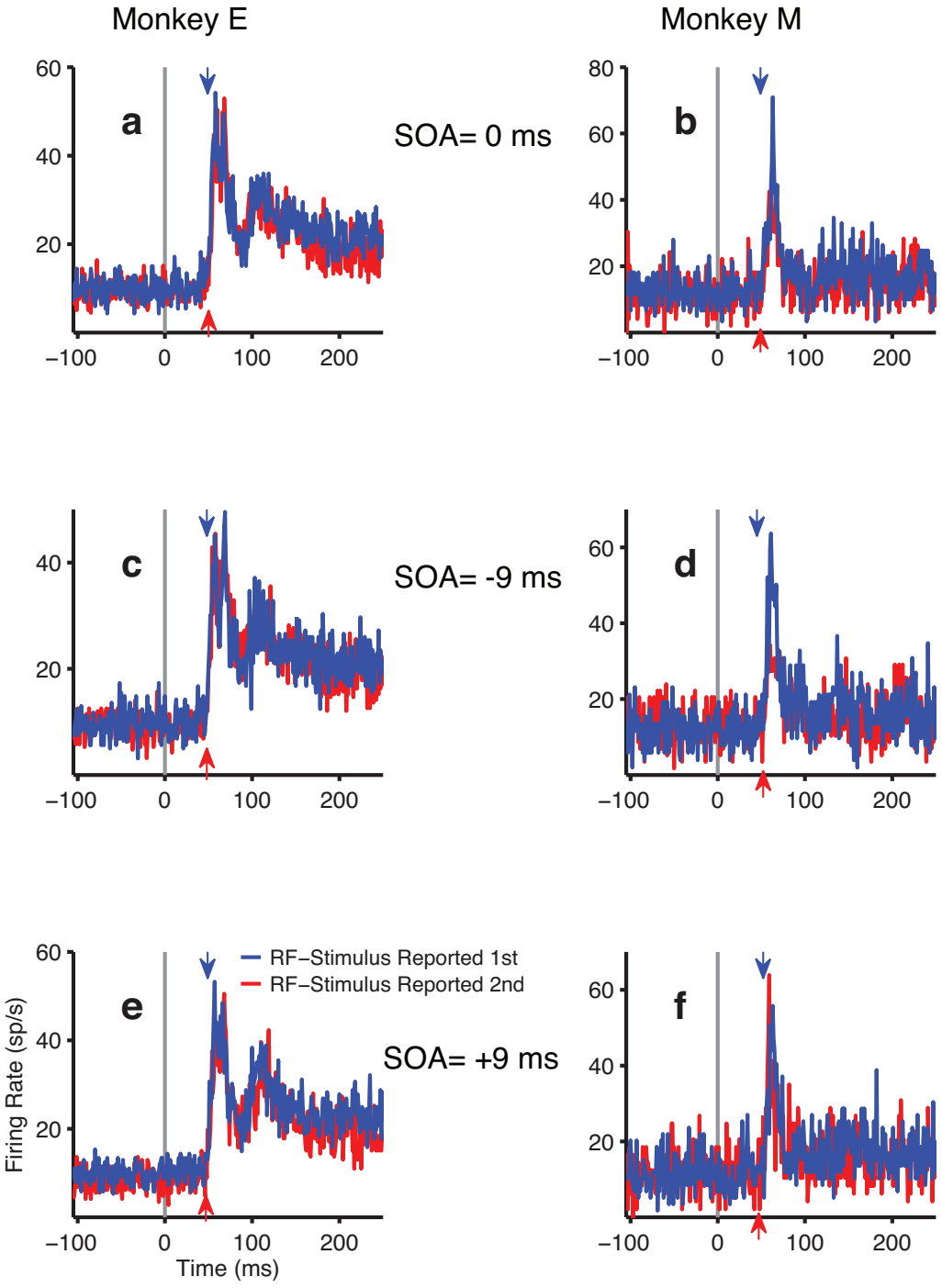


Table 3

Table 3	Latency difference: Report 1st – Report 2nd, *p*-value, number of units included, total units	
	monkey E	monkey M
SOA=0 ms	0.6 ms (p=0.55) 31 (50)	0.9 ms (p=0.7) 11 (16)
SOA= -9 ms	1.2 ms (p=0.09) 33 (50)	- 3.6 ms (p=0.18) 11 (16)
SOA= +9 ms	-0.8 ms (p=0.3) 35 (50)	4.9 ms (p=0.053) 9 (16)

Table 3. Mean latency differences across population. Difference (report 1st – report 2nd), *p*-value (significance of distribution different from 0, t-test, two-tailed), number of units included in the latency analysis and total number of units is shown. Mean latency difference and *p*-value are shown on the first row in each table cell, whereas number of units included and total number of units are shown on the second row. Values are shown for each SOA (0 ms, -9 ms, + 9 ms) and each monkey separately.

Table 4

Table 4		Latency across all units: Report 1st vs. Report 2nd, 95% confidence interval	
		monkey E	monkey M
SOA=0 ms	Report 1st	49 ms (48-51 ms)	49 ms (35-51 ms)
	Report 2nd	50 ms (47-52 ms)	49 ms (33-53 ms)
SOA= -9 ms	Report 1st	48 ms (47-49 ms)	45 ms (43-52 ms)
	Report 2nd	48 ms (47-50 ms)	52 ms (39-55 ms)
SOA= +9 ms	Report 1st	49 ms (48-49 ms)	52 ms (25-54 ms)
	Report 2nd	47 ms (47-51 ms)	47 ms (37-53 ms)

Table 4. Latency calculated across pooled units. Values for each perceptual choice (report 1st vs. report 2nd) are shown alongside with the reliability of the measurement (95% confidence interval based on bootstrapping with replacement). Values for each SOA (0 ms, -9 ms, +9 ms) and each monkey are shown separately.

Table 5

Table 5	Latency difference: Report 1st – Report 2nd, 95% Confidence Interval	
	monkey E	monkey M
SOA=0 ms	-1 ms 95% CI: -2 to 2 ms	0 ms 95% CI: -5 to 16 ms
SOA= -9 ms	0 ms 95% CI: -1 to 1 ms	- 7 ms 95% CI: -10 to 9 ms
SOA= +9 ms	2 ms 95% CI: -2 to 2 ms	5 ms 95% CI: -7 to 9 ms

Table 5. Latency differences calculated across pooled units. The difference (report 1st – report 2nd) is shown alongside the 95% confidence interval (permutation test, 2000 iterations). Values for each SOA (0 ms, -9 ms, +9 ms) and each monkey are shown separately.

3.4 Discussion

3.4.1 LIP units are modulated in a TOJ task

The main finding of our study was that in the temporal order judgment task, LIP units tended to show larger activity when the animal reported that the stimulus in the unit's RF appeared first. This increased activity was most prominent during the tonic period of the response, starting ~100 ms after stimulus onset. Because of the delayed match-to-sample design of the experiment, differences in neuronal firing between the two possible perceptual reports could not have been due to the *way* the animal signaled that report: during the periods of the trial over which we analyzed the neuronal data, the animal did not know whether or not he would release the touch bar at the first color change. Thus the variations in the firing of LIP neurons reflected the trial-by-trial percept of temporal order. These data are at least consistent with parietal neurons playing a role in the perception of visual temporal order – although we have to carefully consider the nature of the parietal neuronal signals.

3.4.2 Considering a "bottom up" explanation

Dating back to the work of Newsome and colleagues (Britten et al., 1996) many experiments have used choice probability to examine the trial-by-trial relationship between cortical neuronal firing and perceptual report. In a sense, our findings are typical: the maximum choice probability for individual neurons was only modestly higher than that expected from chance (0.5). Because CP reflects an ideal observer's ability to

predict the animal's perceptual report from the spike counts, low CP in single neurons suggests that the signals from many neurons must be pooled to determine the final perceptual report (Britten et al., 1996). Implicit in this argument is that there is a *causal* relationship between the neuronal firing and the animal's perceptual report. In this "bottom-up" view, trial-to-trial variations in firing rate constitute sensory noise that is fed forward to influence a subsequent decision stage (Mazurek, Roitman, Ditterich, & Shadlen, 2003).

As a first step, it is instructive to ask how a similar bottom-up model could be applied to our TOJ paradigm. Much of the previous work relating firing of cortical neurons to perception has been based on the paradigm developed by Newsome and colleagues, in which monkeys discriminate the net direction of motion of noisy random-dot kinematograms (two-alternative forced choice). In the model proposed by Shadlen and colleagues (Mazurek, Roitman, Ditterich, & Shadlen, 2003; Shadlen, Britten, Newsome, & Movshon, 1996), the random-dot stimulus would affect two ensembles of neurons with overlapping receptive fields, but with opposite direction preferences. Spike counts would be pooled within each neural ensemble and subsequently integrated and thresholded, as described by a race process (Luce, 1986). The neural pool that reaches threshold earlier would "win" and lead to the percept of the corresponding preferred direction for that neural pool.

In principle, temporal order judgments in the brain could be carried out by a similar competitive race process. The two stimuli could be represented by distinct populations of neurons, with receptive fields at two separate locations, corresponding to the two stimuli of the TOJ paradigm (the actual stimuli were *pairs* of spots, but the

argument can be readily extended to consider pooling between neurons representing both spots in a given pair). Spike counts would be pooled within each neuronal ensemble and subsequently integrated and thresholded, as described by a race process. The neural pool that reaches threshold earlier would lead to the percept of the corresponding stimulus appearing *first*.

In the random-dot kinematogram experiments, the animals typically view the stimulus for hundreds of milliseconds; thus in weighing the perceptual decision, the brain could integrate sensory information for an extended period of time. However, in our TOJ experiment, the animals were able to discriminate temporal order with SOAs as short as a few *tens* of ms. Thus the usable data for the integration and race process must be confined to the narrow interval of the SOA (after accounting for neuronal latency). Once both stimuli have turned on, the neuronal data are no longer informative of which stimulus appeared first. On the other hand, the stimuli themselves were supra-threshold (large, bright spots) and elicited strong neuronal responses, so we might expect that integrated neuronal data could reach threshold very quickly (unlike the weak motion signals in noisy random-dot kinematograms). Thus a bottom up mechanism might be subserved by an integration/race process compressed to the few tens of ms of the SOA.

The implication of this bottom-up model to the TOJ experiment is that the relevant neuronal integration must occur quickly -- on the time-scale of the SOAs. Thus we should expect to see CP during the *earliest* part of the neuronal response following the onset of the stimulus in the RF. In this view, if the response to the RF-stimulus happens to be a little bit larger on a given trial, the neuronal pool corresponding to the RF location should reach threshold a little sooner, and the animal would tend to perceive the

RF-stimulus as appearing first. If instead the RF response happens to be a little smaller, the animal would tend to perceive the RF-stimulus as appearing second. In this view, variations in latency can also be considered variations in the strength of response over a narrow time window. However, we did *not* detect consistent perceptual signals during the earliest part of the visual response (nor did we detect consistent differences in latency). Rather CP became elevated above chance beginning ~100 ms after stimulus onset. Thus at first glance our findings are not consistent with LIP providing a strong bottom-up signal that influences perception. On the other hand, we know very little about how neuronal networks actually instantiate race processes (if indeed race processes occur in the brain), and it is possible that the dynamics of the integration-to-threshold do not necessarily reflect the instantaneous stimulus dynamics. For example, the process must be minimally delayed by the time it takes for the visual signals to reach the neurons performing the integration. Moreover, because in our TOJ experiment the animal must defer its decision, the sensory data could be "buffered" in some way, leading to a race process that unfolds even later in time following the onset of the stimuli. In fact, we recently found evidence for such a deferred decision process in another LIP experiment (Herrington and Assad, 2009). Nonetheless, the late development of the CP in the TOJ experiment suggests that LIP neurons are *not* causal to the animal's perception of temporal order, and could instead reflect a "top-down", post-decisional process (see below).

As a final thought about potential bottom-up processes, it might seem odd to suggest that a neuron that represents only *one* of two stimuli could contribute to a temporal order judgment between the two stimuli. That is, we designed our task so that

only one stimulus was centered in the RF, and in most cases the stimulus outside the RF had no effect on the neuron's response to the RF stimulus. It might seem that a neuron subserving temporal order judgments should have a large RF encompassing *both* stimulus events. However, this does not necessarily follow. For one, random variations in the firing of the two competing neural pools representing one or the other stimulus (but not both) could affect the decision at a later stage of the process. If so, neurons could play a causal role in the percept (and thus have a significant CP) without being "directly" involved in the decision process. For example, in the classic models of perceptual decisions, evidence for one motion direction or the other is processed in distinct MT neuronal pools, whereas the integration takes place downstream in the visual hierarchy (Gold & Shadlen, 2007; Shadlen & Newsome, 2001). Moreover, the integration-to-threshold underlying the race process could also occur in independent pools of decision-related neurons. With a two-alternative forced choice design to ensure an unambiguous behavioral outcome, it seems likely that at some stage the competing neuronal pools should interact in a winner-take-all-manner (perhaps by mutual inhibition), but this could occur outside the visual system (for example in the oculomotor system). Thus there is no a priori reason to expect that the decision mechanism must have a *visual* representation of both stimuli in the TOJ task.

3.4.3 Top-down explanations

Top-down mechanisms have been suggested in the literature to explain at least part of the CP effects seen in different paradigms (Herrington & Assad, 2009; Nienborg

& Cumming, 2006, 2009). Top-down mechanisms could also have a straightforward role in explaining our results. Imagine a trial with SOA=0 ms, in which (for whatever reason) the monkey happened to be attending to the location of RF-stimulus before its appearance on the screen. According to the prior-entry theory (explained in section 1.3), the animal would be more likely to report the RF-stimulus first, because visually attended stimuli are more likely to appear first, a notion that has been supported by human psychophysical studies (Shore et al., 2001; Spence & Parise, 2010; Stelmach & Herdman, 1991). Neurons with their RF at that location would also tend to have a larger response, because spatial attention increases the amplitude of visual responses in LIP (Bisley & Goldberg, 2003; Herrington & Assad, 2009, 2010). If spatial attention causes neuronal responses to be higher *and* leads the animal to report the RF-stimulus appearing first, a CP > 0.5 would be obtained. The same would hold if the animal were attending to the nonRF-stimulus location before any stimulus appeared on the monitor (lower activity at the RF location *and* reporting the RF-stimulus as second), again leading to a CP > 0.5. Thus if the monkey were shifting his spatial attention to different locations from trial to trial, the same results could be obtained. Spatial attention could also explain CPs > 0.5 for SOAs other than zero, inasmuch as attention could overcome the bottom-up temporal offset signal.

In this scenario, the firing of LIP units may or may not be causal to the animal's judgment of temporal order. For example, it is possible that the prior spatial attention has parallel, *independent* effects on the neuronal firing and on the animal's judgment (by affecting some other, causally related pool of neurons). If so, the firing of LIP neurons would not be causal to the animal's percept, even though CP > 0.5. Alternatively, the

prior entry effect on temporal order judgment could be mediated (at least partially) *through* the effect of spatial attention on LIP neurons. If so, LIP firing would be causal to the animal's judgment.

Regardless of the question of causality, in the prior entry scenario, one might expect higher *baseline* activity on trials in which the animal subsequently reported the RF stimulus appearing first. However, only a small percentage of our units showed significant CPs larger than 0.5 during the baseline period (highest percentage among all three SOAs, 0 ms, -9 ms, +9 ms: monkey E, 8%; monkey M, 6%). Neither did we observe the distribution of CPs significantly larger than 0.5 in any CP histogram calculated for the baseline period (three SOAs in two monkeys). Although the reported magnitude of attentional effects on baseline activity has been small, some researchers have found consistent and reliable effects, at least in the ventral visual pathway (Lee et al., 2007; Luck, Chelazzi, Hillyard, & Desimone, 1997; Reynolds et al., 2000; Williford & Maunsell, 2006). It would be useful to examine baseline activity with more sensitivity in future TOJ experiments, perhaps by having fewer SOAs and more trials per SOA.

The prior entry explanation for our results is a "top-down" explanation that is pre-decisional, in that spatial attention to one location or another would influence the animal's temporal judgment. Alternatively top-down effects might also indicate a *post-decisional* process. That is, the judgment of temporal order could be performed in another cortical area, and the perceptual effect we observed in LIP is simply a reflection of that process. For example, during a trial when the animal figures out which pair has appeared first, he could rapidly divert spatial attention to that pair, monitoring it to react as soon as possible when it turns green. Spatial attention would thus tend to increase the neuron's

activity when the RF-stimulus appears first. In the other half of trials in which the nonRF-stimulus appears first, the nonRF-stimulus would capture the animal's spatial attention, diverting attention away from the RF location, and thus decreasing neuronal activity. The combination of these trials would also lead to CPs larger than 0.5, consistent with our data, but by definition, such a post-decisional signal would not be causal to the animal's judgment of temporal order.

In this scenario, even if attention does not directly affect the judgment of temporal order, attention could be useful for carrying out the task. For example, because in our TOJ experiment the animals had to defer their responses in time, the animal had to have some way to "tag" the first stimulus pair that appeared. In fact, some errors could have been due to the animal's attention drifting away from the first pair before the color change --- an effect that would have also contributed to the measured CP.

The strongest perceptual effects we observed were during the tonic period of the response, consistent with the view that the perceptual modulation could be a post-decisional process. In our dataset a few neurons (monkey E: 12%, monkey M: 6%) showed significant CPs larger than 0.5 during the phasic period (SOA=0 ms). It is plausible that these cells have a more direct role in the animal's temporal order judgment.

The foregoing discussion of the potential effects of attention during our relative timing task suggests that results from other timing tasks should also be interpreted cautiously. For example, Leon and Shadlen trained animals to report whether the duration of a test stimulus was longer or shorter than a reference stimulus by making an eye movement to one of two choices (short-choice and long-choice targets) (This experiment

examined the neuronal correlates of *elapsed* time rather than relative time, but similar concerns apply). The authors found that activity of LIP neurons gradually changed with the passage of time: at the beginning of the test stimulus the activity favored the short-choice target, whereas this preference gradually gave way to the long-choice target if the test stimulus was sufficiently prolonged (Leon & Shadlen, 2003). Based on these findings, the authors suggested that LIP neurons encode elapsed time. However, their data is also fully compatible with an attention-switching explanation, in which the animal attends first to the short-choice target and gradually shifts attention to the long-choice target as the test stimulus is prolonged.

In summary, we found neuronal signals in LIP that reflect the animal's temporal order judgment – but we must be cautious in interpreting those results. The late development of CP following the onset of the visual stimulus in the RF is suggestive of a post-decisional effect. However, it is also possible that we lacked sufficient sensitivity to detect earlier neuronal signals related to temporal judgments. For example, it has generally been difficult to detect attentional effects on baseline activity (which might otherwise reflect evidence for a prior entry effect in our data). Moreover, we expected it to be difficult to detect CP during the brief visual transient, although there were hints in our data set that such effects might also be present during the visual transient. Future experiments could be designed to better detect potential effects during these time periods. Finally, we should also point out that the various potential explanations for the origin of the CP are not mutually exclusive. The CP could reflect a mixture of influences even at the level of a single cell, including bottom-up effects, effects of prior entry and post-decisional effects (Herrington and Assad, 2009).

3.4.4 Latency effects in the visual system

There are a few reports in the literature suggesting that visual response latency could be used as a coding mechanism in the visual system. For example, stimuli of higher contrast show lower visual latency, both in V1 and V4 (Lee et al., 2007; Reich, Mechler, & Victor, 2001). In addition, different viewing angles of faces as well as human vs. non-human primate faces show different response latencies in the inferotemporal cortex (Eifuku, De Souza, Tamura, Nishijo, & Ono, 2004; Kiani, Esteky, & Tanaka, 2005). As long as latency varies among stimuli, it is conceivable that latency could be used, at least in part, to distinguish or code those stimuli. One way to test this hypothesis is to ask whether latency and perception vary in concert from trial to trial -- ideally with other visual parameters held fixed. Our TOJ experiment provides such an opportunity. Moreover, it seems reasonable that response latencies (rather than response amplitude) might be related to perception of temporal order, because the essence of temporal order judgment is presumably determining the precise time of onset of stimuli. For example, if the response latency to a visual stimulus is particularly brief on a given trial, that stimulus might be more likely to be perceived as appearing first.

With respect to visual latency, while we observed examples of units showing earlier responses when the RF-stimulus was reported first (e.g., Figures 6, 7 and 8), we did not find any significant difference at the population level. However, it is plausible that we could not detect any difference due to low statistical power: latency analyses typically require averaging over hundred(s) of trials per condition (Kiani et al., 2005), and our experimental design was not tailored to such specifications; Our paradigm was

designed to enable us fully capture the animal's behavioral performance and sample the full range of 11 SOAs rather than to sample any single SOA exhaustively.

3.4.5 Surround Modulation

Although surround modulation has been well established in low-level visual areas such as V1 (J. R. Cavanaugh, Bair, & Movshon, 2002), V4 (Desimone & Schein, 1987; Sundberg, Mitchell, & Reynolds, 2009) and MT (Allman, Miezin, & McGuinness, 1985a, 1985b; Born, 2000; Born & Tootell, 1992), it has only recently gained attention in higher visual areas, or in areas suggested to be involved in "saliency-based" representations, such as LIP, the frontal eye field (FEF), and the superior colliculus (SC) (Goldberg et al., 2006; Keller & McPeek, 2002; Thompson & Bichot, 2005). Recent studies have demonstrated surround modulation in FEF and SC (J.R. Cavanaugh, Joiner, & Wurtz, 2012; Churan, Guitton, & Pack, 2012).

Part of the oversight could be due to the fact that these areas have been traditionally studied in the context of saccadic eye movements and covert attention, and less as visual areas with characteristics of other (low-level) visual areas. Accordingly, researchers have focused more on the "response-field" (alternatively called movement-field) of these neurons rather than their "receptive field" (Bruce & Goldberg, 1985; Hikosaka & Wurtz, 1983a, 1983b; Schiller & Koerner, 1971; Shadlen & Newsome, 2001; Wurtz & Goldberg, 1971).

Goldberg and colleagues have recently shown surround suppression in LIP (Falkner et al., 2010), although the modulation they observed was in the context of making saccades rather than visual-visual interactions: when the animal had to make a saccade to a target outside the RF, the response of a flashing stimulus in the RF was suppressed, compared to the no-saccade control.

Our task did not require a saccade; thus it is tempting to assume that the surround effects we observed were due to visual-visual interactions. However, it is also possible that the surround modulation was a consequence of attention. Although the interactions we observed seem too fast for endogenous shifts of attention (Herrington & Assad, 2009), the time-course of surround-suppression in LIP seems compatible with exogenous attention (Bisley & Goldberg, 2003; Muller & Rabbitt, 1989; Nakayama & Mackeben, 1989). In this view, once the first stimulus appeared, the animals could have quickly shifted attention to that location to monitor whether the stimulus turned green later in the trial. In addition, the animals were extensively trained and presumably highly motivated to shift attention within the context of the task. For this reason, it would be interesting to examine whether surround-suppression is a general property of LIP units that is also observed in experimentally naïve animals, or rather a property that emerges only after training on tasks in which specific locations become behaviorally salient, such as in our timing task.

3.4.6 Categorization Framework

It has been proposed that LIP might have a more general role as representing categorical information in the visual system. Previous work has shown that when animals were trained to make associations between visual stimuli and group them into different categories (continuous directions of motion in one study, arbitrary pairs of shapes in another study), LIP activity reflected the categorical associations: neuronal responses to exemplars within each category were more similar than between categories (Fitzgerald, Freedman, & Assad, 2011; Freedman & Assad, 2006). This framework could be extended to previous work on perceptual decision-making in LIP (Freedman & Assad, 2011). In those experiments, the animals were required to make perceptual decisions regarding the net direction of noisy motion stimuli (moving leftward versus rightward) by making a saccadic eye movement to the corresponding side (Gold & Shadlen, 2007; Shadlen & Newsome, 2001). However the same task can be viewed as the animal categorizing the motion stimuli with different levels of coherence into two categories -- leftward motion versus rightward motion. The same could be proposed for the temporal order task. The animal was required to group the visual stimuli into two categories -- stimuli appearing first vs. stimuli appearing second. However, a categorization framework does not necessarily explain the mechanism through which the perceptual decision is made, but rather the end result of the categorization or decision process. In addition, a categorization framework cannot act as a universal means of solving the task since each category (appearing first vs. second) is not fixed across trials (in contrast to random-dot motion categories or arbitrarily associated pairs), but depends on the spatial configuration

of each trial. In other words the categorical activity (report first vs. second) cannot be linked in any straightforward way to temporal order of the stimuli in external space.

3.4.7 Differences between the two animals

We observed differences between the two animals regarding the strength of the observed effect. Average CP calculated from the tonic period of the response in monkey E was significantly different from 0.5 for all three stimulus conditions (SOA= -9 ms, 0 ms and +9 ms) as well as for the grand CP pooled across all stimulus conditions, but average CP from monkey M was not statistically significant from 0.5 in any time period (Figures 10-12, Tables 1-2). The main reason for this difference is likely to be that we were able to collect usable data from only 16 units in monkey M, and thus lacked statistical power across the population. In addition, monkey M's behavior was not as good as that of monkey E (percent correct trials: monkey E, 70%; monkey M, 63%), and was more biased across sessions (mean absolute bias: monkey E, 14 ms; monkey M, 31 ms; Wilcoxon-rank-sum test: p=0.01; std of bias: monkey E, 21 ms; monkey M, 42.5 ms). In addition the SOAs presented to monkey M were shorter (and thus more difficult) than those presented to monkey E, making him less motivated and more likely to show behavioral biases. Another possibility is that the data from each animal could have been collected from different sub-divisions of LIP. For example, the visual evoked responses were weaker in units from monkey M compared to those from monkey E. A combination of these factors could underlie the differences observed between the two animals.

3.5 Conclusion

Our experiments demonstrate a neural correlate of temporal order judgment in LIP. When the animals reported the stimulus in the RF as appearing first, LIP cells tended to show an increased level of activity compared to when the animal reported the same stimulus as appearing second. This differential activity was observed when the stimuli were presented simultaneously as well as when there was only one intervening video frame (± 9 ms), and was most reliable in the tonic period of the response. These data are consistent with parietal neurons being involved in the perception of visual temporal order.

However, our data is also compatible with a top-down explanation in which spatial attention can bias the animal's temporal order judgment and at the same time increase the amplitude of the visual response, leading to CP values above 0.5. Yet, we did not detect higher baseline activity when the animal reported the RF-stimulus first, an expected consequence of the top-down explanation. Nonetheless, the late effect that we observed could be a sort of attentional "tagging" of the first stimulus perceived. In this view, parietal cortex could play a critical role in temporal order judgments even if it is not directly involved in the initial detection or discrimination of the first stimulus to appear.

The parietal cortex has been previously implicated in TOJ tasks. Imaging studies, temporary disruptive techniques as well as patient studies point to the involvement of parietal cortex in temporal order judgments (G. C. Baylis et al., 2002; Davis et al., 2009; Rorden et al., 1997; Sinnett et al., 2007; Woo et al., 2009). However, it is not clear how

the parietal cortex is involved in temporal judgments. One possibility could be through its general role in temporal attention, where the right parietal cortex is involved in identifying transients, assigning them as onset vs. offset transients and subsequently linking them into temporally defined objects in both visual hemifields (Battelli et al., 2001; Battelli et al., 2003). However, the nature of a TOJ task does not seem to rely on onset/offset assignments. In addition, in patients with TOJ deficits lesions are not restricted to the right side, in contrast to the "when" pathway proposed by Battelli and colleagues (Battelli et al., 2007; Battelli et al., 2008). Another explanation could be the role of parietal cortex in spatial attention, as patient's deficits in the TOJ task resembles that of visual extinction. Visual extinction, classically associated with parietal damage, is a deficit in which patients can detect or judge a visual event in either hemifield when presented in isolation, yet miss events towards the contralesional side when bilateral stimuli are presented simultaneously (Baylis, Driver, & Rafal, 1993; Bradshaw & Mattingley, 1995; Rorden et al., 1997). Similarly, in TOJ tasks parietal patients often judge two temporally proximate events as the ipsilesional stimulus appearing first. Thus TOJ deficits could be a manifestation of the same spatial deficits in patients with visual extinction. Finally the parietal cortex could be involved in TOJ at the decision level, similar to its role in perceptual decisions described previously (Gold & Shadlen, 2007; Mazurek et al., 2003). In this view, the attentional advantages in temporal order judgment could be explained as a shift in the decision criteria. This view is compatible with the prior-entry theory (Shore et al., 2001; Spence & Parise, 2010), in which attention is seen to affect temporal order judgments. In this framework the TOJ deficits in parietal patients

are a reflection of a criterion shift heavily biased towards the ipsilesional stimuli and leading to a temporal advantage for these stimuli.

Previous work has shown parietal neurons encoding *elapsed* time (Leon & Shadlen, 2003). In our study, we focused on a completely different aspect of timing judgments -- the relative onset of temporal events -- and demonstrated the involvement of parietal neurons in coding relative timing. We conclude that through different computations, LIP neurons could encode different aspects of time perception.

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Chapter 4

General Conclusion

Timing computation is considered as one of the most important aspects of information processing in the mammalian brain. This computation can be regarding implicit timing, where time is an inherent part of the computation or explicit timing where the perception of time is crucial as well.

The dissertation looks at two different aspects of timing judgments. Both studies focus on relative timing, that is making judgments regarding instants of time: in the first study, onsets/offsets of two flickering dots had to be perceived and judgments made regarding their relative phase in human subjects. In the second study onsets of two pairs of stimuli had to be compared and the one perceived as first reported. The second study focused on an animal model (Macaca mulatta) and neural activity was collected as well as behavioral data.

In the first study, we looked at the temporal limits of phase discrimination across the visual field (Aghdaee & Cavanagh, 2007). When two flickering dots are close enough, their relative phase can be judged based on the low-level motion signal between them. However as they become farther apart, the contribution of low-level motion decreases, and relative phase judgments rely on the temporal individuation of light and dark phases of each dot. If individual phases of each flickering dot cannot be accessed, the relative timing between them is lost, and no linking of their phase across the space is possible, making relative phase judgments impossible. At the farthest separation between the two dots, we investigated the highest rate at which individuation can still be maintained, also known as Gestalt flicker fusion (Van-deGrind, Grüsser, & Lunkenheimer, 1973). This rate has been proposed as the "temporal resolution of attention": beyond this rate, one can easily distinguish a flickering dot from an

isoluminant dot, but one cannot discern the onset and offset of each dot, a property attributed to temporal properties of attention (Battelli et al., 2001; Verstraten, Cavanagh, & Labianca, 2000). We measured this individuation rate as a function of inter-dot separation at two different eccentricities (4° vs. 14°), and upper vs. lower visual field. We found that the threshold for phase judgments at the largest inter-dot separation (where there is little contribution of low-level motion) decreased by ~30% (11.4 vs. 8.9 Hz) with increased eccentricity (4° vs. 14°). In addition, we found no difference between the thresholds for the upper and lower visual fields. These characteristics of temporal attention are markedly different from those of spatial attention. The spatial resolution of attention (minimum spacing between items for them to be individuated) is noticeably finer in the lower visual field than the upper field (17-50% advantage for items in the lower visual field (Intriligator & Cavanagh, 2001)), in contrast to what we found for temporal attention. The advantage of foveal presentation is even more pronounced for spatial individuation compared to temporal individuation: while we found a 30% advantage for more foveal stimuli, Intriligator and colleagues found an advantage of almost 300% over a similar range of eccentricities (Intriligator & Cavanagh, 2001).

From the first study we conclude that temporal and spatial individuation of visual items have very different properties across the visual field. Assuming individuation is mediated through attention, the umbrella term "attention" exhibits different properties, at least in the space and time domain, with presumably different underlying circuits. These observations underscore the necessity of having an operational definition of attention every time it is used, with particular emphasis on which aspect of attention (feature, space, time) is under study.

In the second study we trained two monkeys on a Temporal Order Judgment (TOJ) task and looked for neural correlates of such judgments while the animals were engaged in the task. We recorded from single neurons in the lateral intraparietal area (LIP) while the animal reported the perceived temporal order of two visual stimuli, presented with variable stimulus onset asynchronies (SOAs) in between. Unbeknownst to the monkey, each session also included trials in which the stimuli were presented simultaneously (SOA=0). On these trials, there was no bottom-up information to guide the animal's perceptual choice. We then looked at the neural activity based on whether the animal reported the stimulus in the receptive field (RF) as appearing first or second. We found that LIP neurons show differential activity based on the animal's perceptual report: when the animal reports the stimulus in RF as appearing first, the cells show an increased level of activity compared to when the animal reported the same stimulus as appearing second. This differential activity was most reliable in the tonic period of the response (~100 ms after stimulus onset). However, no difference in visual response latencies was observed between the different perceptual choices.

In the second study, we found a neural correlate of temporal order judgments in the parietal lobe. Neuropsychological and imaging studies had suggested the involvement of the parietal cortex in TOJ tasks; neurophysiological studies had also suggested a role for parietal neurons in coding *elapsed* time (Leon & Shadlen, 2003). However, to our knowledge our study is the first to examine the involvement of parietal neurons in encoding *relative* timing. We conclude that through different computations, LIP neurons can encode different aspects of timing judgments.

Since the two studies look at different tasks for relative timing judgments, and in particular, in two different groups of subjects (humans vs. monkeys) it is difficult to make direct comparisons. However, some aspects of the behavioral data might give us some insights.

In the first study, thresholds for phase discrimination were studied for flickering dots. Subjects had to judge the relative phase of two flickering dots, reporting whether they are in-phase or out-of-phase. One way subjects could have performed the task is through simultaneity judgments, i.e. whether they perceived the onset/offset of the two flashes happening at the *same* time or not. In addition, observers could have used (high-level) apparent motion at the farthest disc separations to make the phase judgments. However, regardless of which strategy (or strategies, and how much of each) they used, observers' thresholds at 75% correct were about 9-11 Hz at the farthest separation. In comparison in the TOJ task, animals had to report the relative onset of two visual stimuli. Due to the design of the task, motion information, if any, could not help the animal perform the task. Yet the animals' thresholds (82 % of maximum performance) were 34 and 41 ms for monkey E and monkey M, respectively. This is more than two-fold faster than that obtained for human subjects in the first study.

There could be different reasons for this discrepancy. First, the two tasks might be different enough for a direct comparison. The phase-discrimination task requires observers to individuate each flickering spot and then compare the relative phase of the two spots. On the other hand, the TOJ task does not seem to require individuation of on/off states of each stimulus, but simply comparing the onsets. Second, the TOJ task was studied in highly motivated animals extensively trained for months, where the

thresholds improved until a steady level achieved. It is interesting to investigate whether the temporal limits of individuation are fixed or also show plasticity with extensive training.

The thresholds obtained from humans in the TOJ task are larger than those we obtained from monkeys after the training period, even though The TOJ task in humans can also be performed through perception of long-range apparent motion (in contrast to our task), offering an advantage to human subjects in performing order judgment. From human psychophysics studies, thresholds and *Just-Noticeable Difference* (JND) for the TOJ task can be estimated (JND defined as the temporal difference corresponding to half of the interquartile range). Subjects in the study by Woo and colleagues report thresholds, (corresponding to 80% probability of reporting one stimulus first) between 70-80 ms, with JND values around 50 ms, estimated from their figure 3 (Woo et al, 2009). In our study, early in the course of training the animals, we observed thresholds similar to those reported for human observers. However, as training pursued, the animal's performance improved leading to a decrease in thresholds. We consider this difference due to the extent of training in our animals. Thus caution must be exerted when making comparisons between humans and monkeys in the task since the stimulus configuration used in our study was vastly different from those used in humans in addition to the huge improvement we observed, most likely due to prolonged training.

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